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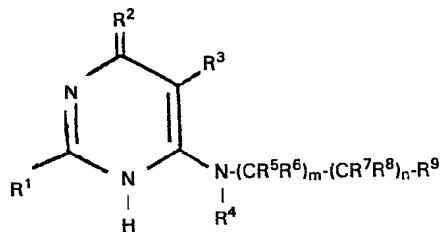
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⑤ Amino-pyrimidine derivatives.

⑦ The invention concerns compounds of the formula I



benzthiazolyl, benzoxazolyl, benzpyranyl, isoindolyl, or indolaziny; and m and n each independently is an integer 0 to 2; or a therapeutically acceptable addition salt thereof for use in increasing cardiac contractility in mammals. Processes for their preparation and pharmaceutical compositions containing them also disclosed.

in which R¹ is lower alkyl, cyclo(lower)alkyl, phenyl(lower)alkyl, or trifluoromethyl; R² is oxo, thioxo or imino; R³ is cyano, aminocarbonyl, nitro, methylsulfonyl or aminosulfonyl; R⁴, R⁵, R⁶, R⁷ and R⁸ each independently is hydrogen or lower alkyl; R⁹ is hydrogen, lower alkenyl, 1-piperidiny, 1-pyrrolidinyl, 1-piperazinyl, lower alkynyl, cyclo(lower)alkyl, 2, 3 or 4-pyridinyl, 2 or 3-furanyl, 2 or 3-indolyl, 2 or 3-thienyl, 5-imidazolyl, 4-morpholinyl, phenyl, phenyl mono- or disubstituted with hydroxy or lower alkoxy, 4-thiomorpholinyl, pyrazinyl, pyridiazinyl, triazinyl, pyrrolyl, pyrazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, isoxazolyl, furazolyl, oxathiazolyl, quinolinyl, isoquinolinyl, pyridopyrimidinyl, benzoxazolyl, benzimidazolyl,

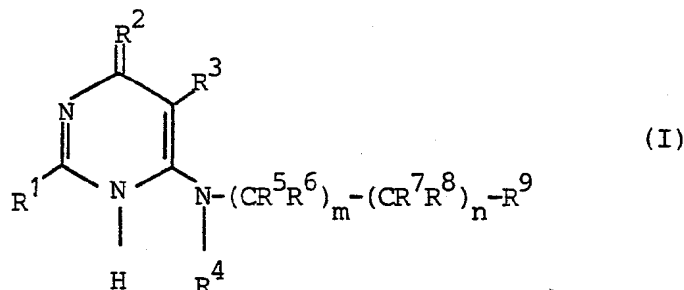
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This invention relates to pharmaceutical compositions containing aminopyrimidine derivatives, to the use of such derivatives and processes for preparing them, to the novel aminopyrimidine derivatives themselves, to intermediates useful in the preparation of the derivatives and to their preparation. The amino-pyrimidine derivatives are useful as cardiotonic agents for increasing cardiac contractility.

A number of pyrimidines and 4-oxopyrimidines are described, for example, B.Rogge et al., Chem. Abstr. 81, 25691m (1974) for East German patent 101,894, November 20, 1973; S.Kisaki et al., Chem. Pharm. Bull., 22, 2246 (1974); Derwent Publications Ltd., Farmdoc 62457W for German Offenlegenshift 2,410,650, published September 11, 1975; Derwent Publications Ltd., Farmdoc 05783J for Japanese Patent 7,176,981, published October 10, 1982; Derwent Publications Ltd., Farmdoc 10368U for Netherland Patent 7,210,637, published February 6, 1973; Chemical Abstracts, 75,49129m (1971) for Japanese Patent 7,108,698, published March 5, 1971; A.Kumar et al., Synthesis, (9), 748 (1980); Derwent Publications Ltd., Farmdoc 46076R for East German Patent 72,790, published May 5, 1970; and Derwent Publications Ltd., Farmdoc 31812R for British Patent 1,189,188 published November 9, 1966. The pyrimidines described in the above reports are distinguished from novel compounds of this invention by the different substituents on the pyrimidine ring and the reported biological activity. Novel amino-pyrimidine derivatives of this invention are also distinguished from the cardiotonic pyridinones, exemplified by G.Y. Leshner et al., United States Patent 4,072,746, February 7, 1978 and G.Y. Leshner et al., United States Patent 4,313,951, February 2, 1982, by having different rings and different substitution on the rings.

Most of the 6-amino-5-pyrimidinecarbonitrile derivatives for which a novel use is claimed in this invention are described by Derwent Publications Ltd., Farmdoc 46076R for East German Patent 72,790, published May 5, 1970 as chemical intermediates for the production of physiologically active substances. Accordingly in one aspect this invention provides a pharmaceutical composition comprising a compound of formula I



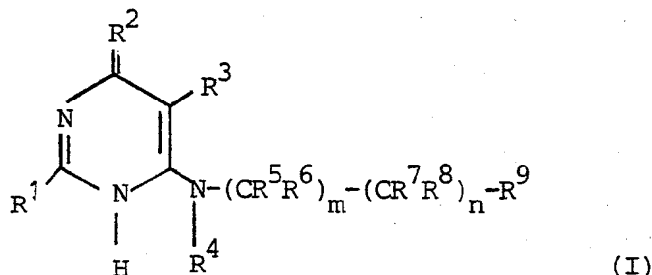
in which R¹ is lower alkyl, cyclo(lower)alkyl, phenyl(lower)alkyl, or trifluoromethyl; R² is oxo, thioxo or imino; R³ is cyano, aminocarbonyl, nitro, methylsulfonyl or aminosulfonyl; R⁴, R⁵, R⁶, R⁷ and R⁸ each independently is hydrogen or lower alkyl; R⁹ is hydrogen, lower alkenyl, 1-piperidinyl, 1-pyrrolidinyl, 1-piperazinyl, lower alkynyl, cyclo(lower)alkyl, 2,3 or 4-pyridinyl, 2 or 3 -furanyl, 2 or 3 -indolyl, 2 or 3-thienyl, 5-imidazolyl, 4-morpholinyl, phenyl, phenyl mono- or disubstituted with hydroxy or lower alkoxy, 4-thiomorpholinyl, pyrazinyl, pyridazinyl, triazinyl, pyrrolyl, pyrazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, isoxazolyl, furazolyl, oxathiazolyl, quinolinyl, isoquinolinyl, pyridopyrimidinyl, benzoxazolyl, benzimidazolyl, benzthiazolyl, benzoxazinyl, benzpyronyl, isoindolyl, or indol-azinyl; and m and n each independently is an integer 0 to 2; or a therapeutically acceptable addition salt thereof.

In a second aspect this invention provides a compound of formula I as defined above or a therapeutically acceptable addition salt thereof for use as a pharmaceutical.

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The novel compounds of this invention are represented by formula I



in which R^1 is lower alkyl, cyclo(lower)alkyl, phenyl(lower)alkyl, or trifluoromethyl; R^2 is oxo, thioxo, or imino; R^3 is cyano, amino-carbonyl, nitro, methylsulfonyl, aminosulfonyl; R^4, R^5, R^6, R^7 and R^8 each independently is hydrogen or lower alkyl; R^9 is hydrogen, lower alkenyl, 1-piperidinyl, 1-pyrrolidinyl, 1-piperazinyl, lower alkynyl, cyclo(lower)alkyl, 2,3 or 4-pyridinyl, 2 or 3-furanyl, 2 or 3-indolyl, 2 or 3-thienyl, 5-imidazolyl, 4-morpholinyl, phenyl, phenyl mono- or disubstituted with hydroxy or lower alkoxy, imidazolyl, 4-thiomorpholinyl, pyrazinyl, pyridazinyl, triazinyl, pyrrolyl, pyrazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, isoxazolyl, furazolyl, oxathiazolyl, quinolinyl, isoquinolinyl, pyridopyrimidinyl, benzoxazolyl, benzimidazolyl, benzthiazolyl, benzoxazinyl, benzpyronyl, isoindolyl, or indolazinyl; and m and n each each independently is an integer 0 to 2; or a therapeutically acceptable addition salt thereof with the proviso that when R^1 is lower alkyl, cyclo(lower)alkyl or benzyl, R^2 is oxo or thioxo; R^3 is cyano; R^4 is lower alkyl, and m and n are both 0 then R^9 is other than hydrogen.

A preferred group of compounds of this invention is represented by formula I in which R^1 is lower alkyl, cyclo(lower)alkyl or benzyl; R^2 is oxo, thioxo or imino; R^3 is cyano or aminocarbonyl; R^4, R^6 and R^8 each independently is hydrogen or lower alkyl, R^5 and R^7 are hydrogen; R^9 is lower alkenyl, cyclo(lower)alkyl, 2,3 or 4-pyridinyl, 2 or 3-furanyl, 2 or 3-indolyl, 2 or 3-thienyl, 4-morpholinyl, phenyl or phenyl mono- or disubstituted with hydroxy or lower alkoxy; and m and n each independently is an integer 0 to 2; or a therapeutically addition salt thereof.

A more preferred group of compounds of this invention is represented by formula I in which R¹ is lower alkyl, cyclo(lower)alkyl or benzyl; R² is oxo or thioxo; R³ is cyano; R⁴, R⁵ and R⁷ are hydrogen; R⁶ and R⁸ each independently is hydrogen or lower alkyl; R⁹ is lower alkenyl, 2, 3 or 4-pyridinyl, 2-furanyl, 3-
5 indolyl, 3-thienyl, 4-morpholinyl, phenyl or phenyl mono- or disubstituted with lower alkoxy; and m and n each independently is the integer 0 or 1; or a therapeutically acceptable addition salt thereof.

This invention also relates to the use for increasing cardiac contractility of a prior reported group of compounds of formula I in which R¹ is
10 lower alkyl, cyclo(lower)alkyl or benzyl; R² is oxo or thioxo; R³ is cyano; R⁴ is lower alkyl; R⁹ is hydrogen, and m and n is each the integer 0 or a therapeutically acceptable addition salt thereof.

A preferred group of compounds for increasing cardiac contractility is represented by formula I in which R¹ is lower alkyl, cyclo(lower)alkyl or benzyl;
15 R² is oxo; R³ is cyano; R⁴ is lower alkyl; R⁹ is hydrogen and m and n is each the integer 0.

This invention also relates to a pharmaceutical composition comprising a compound of formula I or a therapeutically acceptable addition salt thereof and a pharmaceutically acceptable carrier.

20 This invention also relates to a method for increasing cardiac contractility in a mammal which comprises administering to the mammal an effective cardiotonic amount of a compound of formula I or a therapeutically acceptable addition salt thereof.

Detailed Description of the Invention

25 The term "lower alkyl" as used herein means straight and branched chain alkyl radicals containing from one to six carbon atoms, preferably one to four carbon atoms, and includes methyl, ethyl, propyl, 1-methylethyl, butyl, 1,1-dimethylethyl, pentyl and the like, unless stated otherwise.

The term "lower alkenyl" as used herein means straight chain alkenyl
30 radicals containing from two to six carbon atoms and branched chain alkenyl radicals containing three to six carbon atoms and includes ethenyl, 2-methyl-2-propenyl, 4-hexenyl and the like.

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The term "lower alkynyl" as used herein means straight chain alkynyl radicals containing from two to six carbon atoms and branched chain alkynyl radicals containing four to six carbon atoms and includes ethynyl, 2-propynyl, 1-methyl-2-propynyl, 3-hexynyl and the like.

5 The term "cyclo(lower)alkyl" as used herein means saturated cyclic hydrocarbon radicals containing from three to six carbon atoms and includes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

10 The term "lower alkanol" as used herein means both straight and branched chain alkanols containing from one to four carbon atoms and includes methanol, ethanol, 1-methylethanol, butanol and the like.

15 The term "inorganic proton acceptor" as used herein means the inorganic bases, preferably the alkali methyl hydroxides, alkoxides, carbonates and bicarbonates, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, sodium bicarbonate, potassium carbonate, sodium hydride, sodium methoxide and the like.

The compounds of this invention are capable of forming acid addition salts with therapeutically acceptable acids. The acid addition salts are prepared by reacting the base form of the appropriate compound of formula I with one or more equivalents, preferably with an excess, of the appropriate acid in an organic solvent, for example, diethyl ether or an ethanol-diethyl ether mixture.

These salts, when administered to a mammal, possess the same pharmacologic activities as the corresponding bases. For many purposes it is preferable to administer the salts rather than the basic compounds. Suitable acids to form these salts include the common mineral acids, e.g. hydrohalic, sulfuric or phosphoric acid; the organic acids, e.g. maleic, citric or tartaric acid; and acids which are sparingly soluble in body fluids and which impart slow-release properties to their respective salts, e.g. pamoic or tannic acid or carboxymethyl cellulose. The addition salts thus obtained are the functional equivalent of the parent base compound in respect to their therapeutic use. Hence, these addition salts are included within the scope of this invention and are limited only by the requirement that the acids employed in forming the salts be therapeutically acceptable.

The compounds of formula I in which R^2 is oxo or thioxo are also capable of forming addition salts with sodium or potassium. These salts are prepared by reacting the latter compounds of formula I with one or more equivalents of sodium or potassium, or a strong base of sodium or potassium, for example, sodium hydroxide, potassium t-butoxide, sodium hydride and the like. These salts, like the acid addition salts, when administered to a mammal possess the same pharmacological activities as the corresponding nonsalt compound of formula I.

The compounds of formula I or a therapeutically acceptable addition salt thereof are useful as cardiotonic agents for increasing cardiac contractility in a mammal. The cardiotonic effect is demonstrated in standard pharmacological tests, for example, in causing an increase in the contractile force of the isolated cat papillary muscle and reversal of pentobarbital-induced cardiac failure in the dog.

The compounds of formula I of this invention are used alone or in combination with pharmacologically acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard biological practice. For example, they are administered orally in the form of suspensions or solutions or they may be injected parenterally. For parenteral administration they can be used in the form of a sterile solution containing other solutes, for example, enough saline or glucose to make the solution isotonic.

The tablet compositions contain the active ingredient in admixture with non-toxic pharmaceutical excipients known to be suitable in the manufacture of tablets. Suitable pharmaceutical excipients are, for example, starch, milk sugar, certain types of clay and so forth. The tablets can be uncoated or they can be coated by known techniques so as to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period.

The aqueous suspensions of the compounds of formula I contain the active ingredient in admixture with one or more non-toxic pharmaceutical excipients known to be suitable in the manufacture of aqueous suspensions. Suitable excipients are, for example, methylcellulose, sodium alginate, gum acacia, lecithin and so forth. The aqueous suspensions can also contain one or more preservatives, one or more coloring agents, one or more flavoring agents and one or more sweetening agents.

Non-aqueous suspensions can be formulated by suspending the active ingredient in a vegetable oil, for example, arachis oil, olive oil, sesame oil, or coconut oil, or in a mineral oil, for example liquid paraffin, and the suspension may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. These compositions can also contain a sweetening agent, flavoring agent and antioxidant.

The dosage of the compounds of formula I as cardiotonic agents will vary with the form of administration and the particular compound chosen. Furthermore, it will vary with the particular host as well as the age, weight and condition of the host under treatment as well as with the nature and

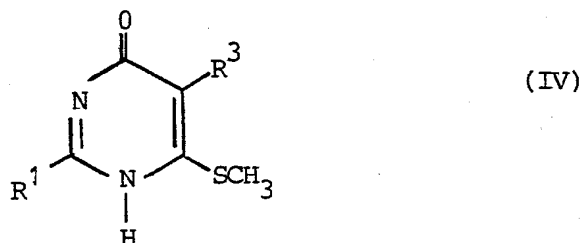
extent of the symptoms. Generally, treatment is initiated with small dosages substantially less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compounds of this invention are most desirably administered at a concentration level that will generally
5 afford effective results without causing any harmful or deleterious side effects. For example, the effective cardiogenic amount of the compounds for oral administration can usually range from about 0.05 to 50 mg per kilogram body weight per day in single or divided doses although as aforementioned variations will occur. However, a dosage level that is in the range of from
10 about 0.2 to 20 mg per kilogram body weight per day in single or divided doses is employed most desirably for oral administration in order to achieve effective results.

The compounds of formula I also can be used to produce beneficial effects in the treatment of congestive heart failure when combined with
15 a therapeutically effective amount of another agent commonly used in the treatment of congestive heart failure. Such agents include, for example: vasodilators, i.e. isosorbide dinitrate, captopril, nifedipine, hydralazine and prazosin; diuretics, i.e. hydrochlorothiazide, furosemide and spironolactone; and other cardiogenics, i.e. digitalis and dobutamine. A combination of
20 the above agents can be substituted for a single agent. Suitable methods of administration, compositions and dosages of the agents are well known in the art; for instance, "Physician Desk Reference", 37 ed., Medical Economics Co., Oradell, N.J., U.S.A., 1983. When used in combination, the compound of formula I is administered as described previously.

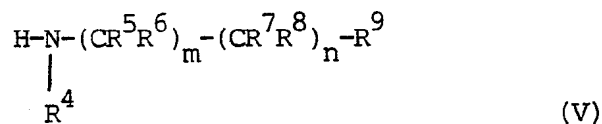
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The invention also provides processes for preparing the compounds of formula I. A first process comprises reacting a pyrimidine IV

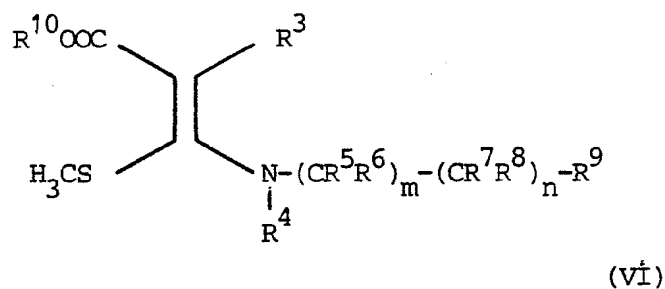


in which R¹ is as defined above and R³ is cyano, nitro, methylsulfonyl or aminosulfonyl with an amine V

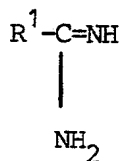


in which R⁴ to R⁹, m and n are as defined above to obtain the compound corresponding to formula I in which R² is oxo and R³ is cyano, nitro, methylsulfonyl or aminosulfonyl and R¹, R⁴ to R⁹, m and n are as defined above. The intermediates of formula IV as defined above are also within the scope of this invention.

A second process comprises condensing a compound of formula VI



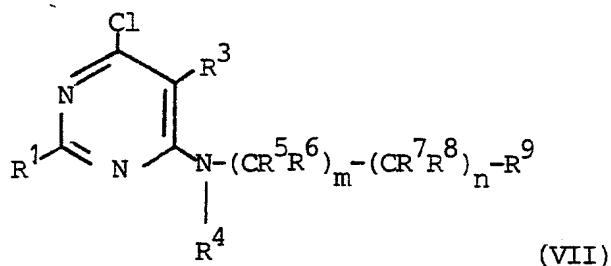
wherein R³ is cyano, nitro, methylsulfonyl or aminosulfonyl, R⁴ to R⁹, m and n are as defined above and R¹⁰ is lower alkyl with an amidine of formula II



II

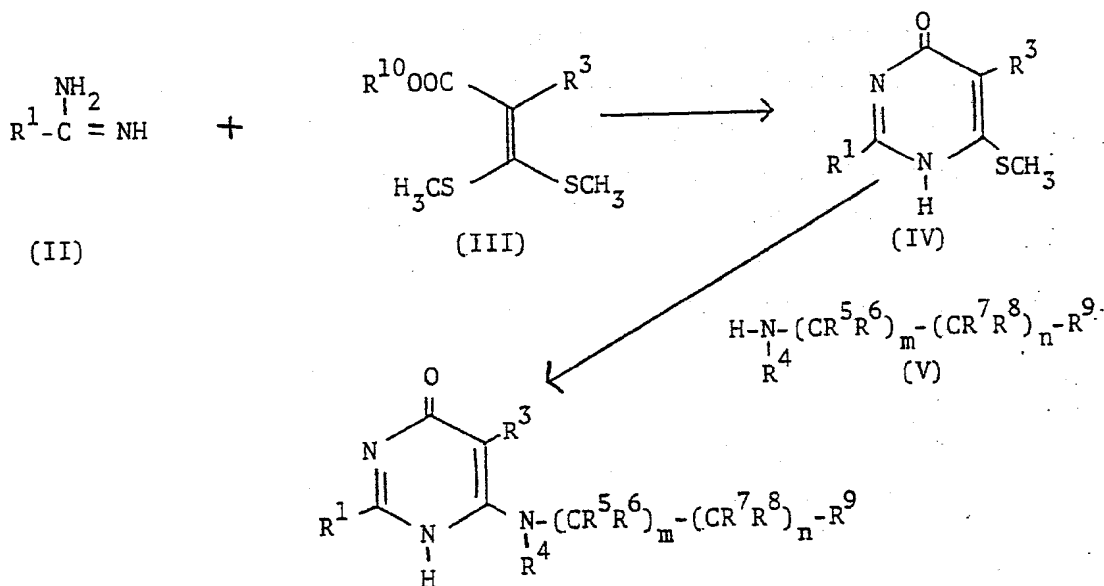
wherein R^1 is as defined above to give a compound of formula I
 wherein R^2 is oxo, R^3 is cyano, nitro, methylsulfonyl or amino-
 sulfonyl and R^1 , R^4 to R^9 , m and n are as defined above.

5 Compounds of formula I wherein X is thioxo may be prepared
 by reacting a compound of formula VII



wherein R^1 , R^4 to R^9 , m and n are as defined above
 and R^3 is cyano, nitro, methylsulfonyl or amino-
 sulfonyl, with an aqueous ethanol solution of potassium hydroxide
 and hydrogen sulfide. Compounds of formula VII as defined above
 10 may be reacted with a solution of an inert organic solvent
 containing an excess of ammonia to give a corresponding compound
 of formula I wherein R^2 is imino.

Reaction scheme I illustrates a method for preparing the
 compounds of formula I

Reaction Scheme 1

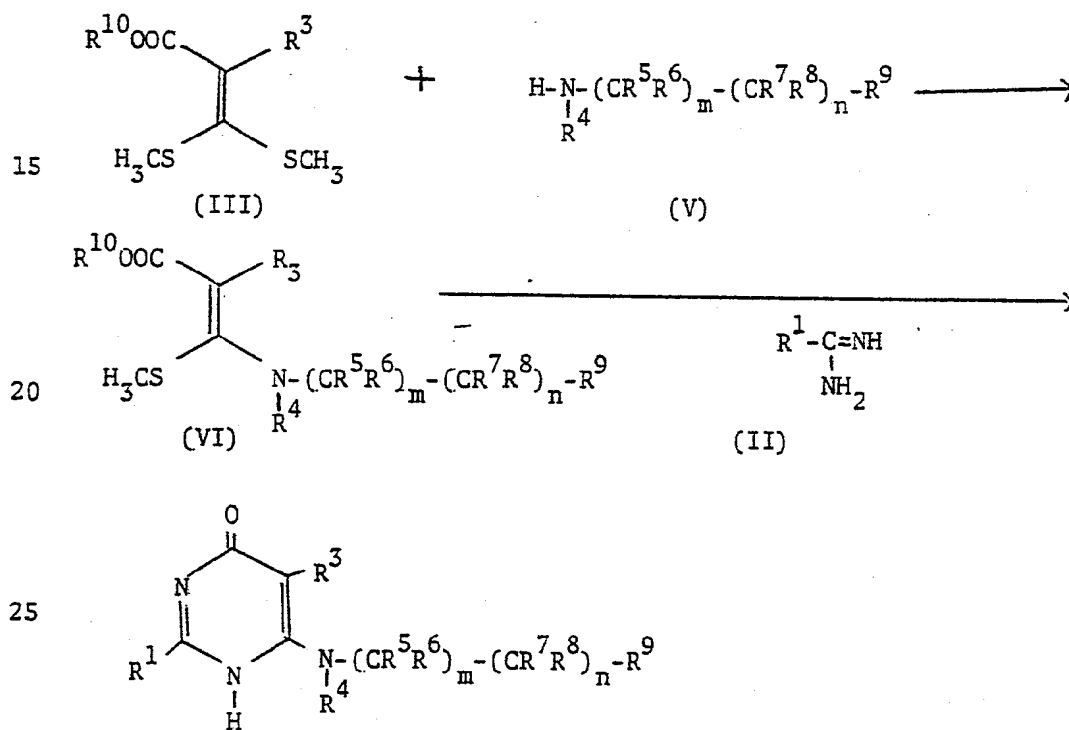
I in which R^2 is oxo and R^3 is cyano, nitro, methylsulfonyl or aminosulfonyl

With reference to reaction scheme 1, the amidine of formula II in which R^1 is as defined herein is condensed with compound of formula III in which R^3 is cyano, nitro, methylsulfonyl or aminosulfonyl and R^{10} is lower alkyl to obtain the pyrimidine of formula IV in which R^1 is as defined herein and R^3 is cyano, nitro, methylsulfonyl or aminosulfonyl according to the method described by S. Kisaki et al., Chem. Pharm. Bull., 22, 2246 (1974). This condensation is preferably achieved by reacting about equimolar amounts of the compounds of formulae II and III in the presence of an inorganic proton acceptor, for example, sodium hydride, sodium alkoxide or potassium carbonate, in an inert organic solvent, for example, ethanol or dimethylformamide, at about 20 to 90° C for about two to ten hours.

Reaction of the pyrimidine of formula IV in which R^1 is as defined herein and R^3 is cyano, nitro, methylsulfonyl or aminosulfonyl with the amine of formula V in which R^4 to R^9 , m and n are as defined herein gives the corresponding compound of formula I in which R^2 is oxo, R^3 is cyano, nitro, methylsulfonyl or aminosulfonyl and R^1 , R^4 to R^9 , m and n are as defined
 5 herein. About one to five equivalents of the amine of formula V are usually used and the reaction is conducted in an inert organic solvent, preferably 1,2-dimethoxyethane, at about 50 to 100° C for about 10 to 30 hours.

Reaction Scheme 2 illustrates another method for preparing some of the compounds of formula I

10 Reaction Scheme 2



I in which R^2 is oxo and R^3 is cyano, nitro, methylsulfonyl or aminosulfonyl

With reference to reaction scheme 2, the compound of formula III in which R^3 is cyano, nitro, methylsulfonyl or aminosulfonyl and R^{10} is lower alkyl is reacted with the amine of formula V in which R^4 to R^9 , m and n are as defined herein to obtain the corresponding compound of formula VI in which R^3 is cyano, 5 nitro, methylsulfonyl or aminosulfonyl and R^4 to R^{10} , m and n are as defined herein. For this reaction, preferably about equimolar amounts of the compounds of formulae III and V are allowed to react at about 20 to 40°C for about ten minutes to two hours in an inert organic solvent, preferably dimethoxyethane, and the compound of formula VI is isolated.

10 Condensation of the compound of formula VI in which R^3 is cyano, nitro, methylsulfonyl or aminosulfonyl and R^4 to R^{10} , m and n are as defined herein with the amidine of formula II in which R^1 is as defined herein gives the corresponding compound of formula I in which R^2 is oxo; R^3 is cyano, nitro, methylsulfonyl or aminosulfonyl; and R^1 , R^4 to R^9 , m and n are as defined 15 herein. When conducting this condensation, preferably about equal molar amounts of the compounds of formula II and VI are condensed at about 75 to 150°C for about 20 to 30 hours in an inert organic solvent, preferably dimethylformamide.

To convert the compound of formula I in which R^2 is oxo to the 20 corresponding compound of formula I in which R^2 is thioxo, the following chemical reactions are required. In the first step, the sodium salt of the compound of formula I in which R^2 is oxo is reacted with an excess of phosphorous oxychloride at about 90 to 120°C for about one to five hours to obtain the corresponding 4-chloropyrimidine derivative. Treatment of the latter 25 derivative with a solution of water and ethanol containing an excess of potassium hydroxide and hydrogen sulfide at about 20 to 40°C for about 20 to 30 hours gives the corresponding compound of formula I in which R^2 is thioxo; R^3 is cyano, nitro, methylsulfonyl or aminosulfonyl; and R^1 , R^4 to R^9 , m and n are as defined herein.

30 Treatment of the above 4-chloropyrimidine with a solution of an inert organic solvent, preferably a lower alkanol, containing an excess of ammonia at about 50 to 80°C for about 20 to 30 hours gives the corresponding

compound of formula I in which R^2 is imino; R^3 is cyano, nitro, methylsulfonyl or aminosulfonyl; and R^1 , R^4 to R^9 , m and n are as defined herein.

Hydrolysis of the compound of formula I in which R^3 is cyano; and R^1 , R^2 , R^4 to R^9 , m and n are as defined herein, preferably with sulfuric acid at about 60 to 100° C for one to ten hours, gives the corresponding compound of formula I in which R^3 is aminocarbonyl; and R^1 , R^2 , R^4 to R^9 , m and n are as defined herein.

The following examples illustrate the preparation of compounds of this invention.

EXAMPLE 1

10 1,4-Dihydro-2-methyl-6-(methylthio)-4-oxo-5-pyrimidinecarbonitrile (IV: $R^1 = \text{Me}$ and $R^3 = \text{cyano}$)

To a suspension of hexane washed sodium hydride (1.46 g, 50% in oil, 1.9 eq) in dimethylformamide (DMF, 1.5 mL) was added dropwise a solution of acetamidine hydrochloride (1.66 g, 1.1 eq) in DMF (7 mL). The reaction mixture was stirred at room temperature for 1 hr. A solution of 2-cyano-3, 3-bis(methylthio)-2-propenoic acid, methyl ester (described by R. Gompper et al., Chem. Ber., 95, 2861 (1962), 3.24 g, 1 eq) in DMF (5 mL, prepared by warming) was added dropwise. Some reaction occurred (evident by gas evolution) during addition. The reaction mixture was allowed to stir at room temperature for 4 hr and diluted with water (13 mL). After acidification with conc. hydrochloric acid (1.5 mL), the precipitate was collected and dried (2.2 g). This was combined with 2.8 g obtained from another such batch and crystallized from DMF (25 mL)/diethyl ether (30 mL), to yield the title compound (3.8 g): mp > 280° C and Anal. Calcd for $C_7H_7N_3OS$: C, 46.39% H, 3.89% N, 23.19% and Found: C, 46.39% H, 3.79% N, 23.27%.

EXAMPLE 2 a) \rightarrow q)

1,4-Dihydro-2-methyl-4-oxo-6-[(3-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile (I: $R^1 = \text{Me}$, $R^2 = \text{O}$, $R^3 = \text{CN}$, R^4 to $R^8 = \text{H}$, m = 1, n = 0 and $R^9 = 3\text{-pyridinyl}$)

30 a) To a solution of 1,4-dihydro-2-methyl-6-(methylthio)-4-oxo-5-pyrimidinecarbonitrile (described in Example 1, 1 eq, 4.4 g) in dimethoxyethane

(33 mL) was added 3-aminomethylpyridine (9.87 mL or 10.53 g, 4 eq). The reaction mixture was refluxed for 18 hours. After about 2 hr of reflux the product started to precipitate. The reaction was cooled after 18 hr and diluted with methanol (12 mL), and the precipitate was filtered. The precipitate was washed with diethyl ether, and dried to yield white solid (5.97 g).

5 A crystallization from hot dimethylformamide yielded the title compound: mp $> 260^{\circ}\text{C}$; Anal. Calcd for $\text{C}_{12}\text{H}_{11}\text{H}_5\text{O}$: C, 59.74% H, 4.60% N, 29.03% and found: C, 59.41% H, 4.75% N, 29.08%; IR (mineral oil) 3320, 2800, 2210, 1660 cm^{-1} ; UV max (MeOH) 289 nm (ϵ 7250); 268 (8300); 263 (8200); 226 (40800); NMR ($\text{DMSO}-d_6$) δ 12.2 (1H, b), 8.5 (1H; b), 8.45 (2H, m), 7.5 (2H, m), 4.6 (2H, d), 2.25 (3H, s).

10 b) A suspension of the title compound (0.120 g, 1 eq) in methanol (1 mL), was stirred with methanolic hydrogen chloride (2N, 1 mL, 4 eq) added to it. The reaction mixture was stirred for 1.5 hr, diluted with diethyl ether (5 mL), and filtered. The solid was washed with diethyl ether, to yield crude product (0.16 g). Crystallization from methanol-water yielded the hydrochloride salt of the title compound (0.1 g): mp $> 250^{\circ}$; and Anal. Calcd for $\text{C}_{12}\text{H}_{11}\text{N}_5\text{O}\cdot\text{HCl}$: C, 51.89% H, 4.32% N, 25.22% and Found: C, 51.81% H, 4.38% N, 25.18%.

c) To a stirred suspension of the title compound (0.491 g, 1 eq) in 20 methanol (2 mL), was added a solution of sodium in methanol (2N, 1.99 mL, 1 eq). The solid went into solution over a period of 0.5 hr. The mixture was stirred overnight during which time some precipitate appeared. Diethyl ether (3 mL) was added, and the sodium salt (0.58 g) was filtered. One crystallization from methanol-diethyl ether yielded the sodium salt of the 25 title compound (0.44 g): IR (mineral oil) 3660, 3630, 3420, 3320, 2850 cm^{-1} ; and UV max (MeOH) 289 nm (ϵ 6680), 267 (7670), 263 (7570), 226 (38050).

d) \rightarrow q) In the same manner, but replacing 3-aminomethylpyridine with an equivalent amount of 3-N-methylaminomethylpyridine, 2-phenylethylamine, 2-(2-pyridinyl)ethylamine, 4-aminomethylpyridine, 2-aminomethylpyridine, 30 benzylamine, 2-aminomethylfuran, N-(2-aminoethyl)morpholine, cyclohexanemethylamine, 3-(2-aminoethyl)thiophene, 2-(3,4-dimethoxyphenyl)ethylamine, 3-(2-aminoethyl)indole, (3-pyridinyl)ethylamine, (4-pyridinyl)ethylamine,

- the following compounds of formula I were obtained, respectively: 1,4-dihydro-2-methyl-6-[N-methyl-N-(3-pyridinylmethyl)amino]-4-oxo-5-pyrimidinecarbonitrile: mp 256-258 °C (cryst. from methanol); IR (mineral oil) 2900, 2200, 1645 cm^{-1} ; UV max (MeOH) 291 nm (ϵ 8490), 269 (9510), 263 (8950), 234 (32200); NMR (DMSO- d_6) δ 11.4 (br, 1H), 8.0 (m, 4H), 4.95 (s, 2H), 3.25 (s, 3H), 2.2 (s, 3H); Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{N}_5\text{O}$: C, 61.16% H, 5.13% N, 27.44% and Found: C, 60.84% H, 5.15% N, 27.37%; 1,4-dihydro-2-methyl-4-oxo-6-[(phenylethyl)amino]-5-pyrimidinecarbonitrile: mp 264-266 °C (cryst. from methanol); NMR (DMSO- d_6) δ 12.0 (br, 1H), 7.8 (t, 1H), 7.2 (m, 5H), 3.55 (m, 2H), 2.8 (t, 2H), 2.2 (s, 3H); Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_4\text{O}$: C, 66.12% H, 5.55% N, 22.03% and Found: C, 66.11% H, 5.60% N, 21.84%; 1,4-dihydro-2-methyl-4-oxo-6-[(2-pyridinylethyl)amino]-5-pyrimidinecarbonitrile: mp 276-278 °C (cryst. from methanol); IR (mineral oil) 3310, 2850, 2220, 1673 cm^{-1} ; Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{N}_5\text{O}$: C, 61.16% H, 5.13% N, 27.43% and Found: C, 60.92% H, 5.15% N, 27.15%; 1,4-dihydro-2-methyl-4-oxo-6-[(4-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile hydrochloride: mp > 250 °C (cryst. from methanol-water); UV max (MeOH) 228nm (ϵ 7110), 255 (8220), 225 (42790); Anal. Calcd for $\text{C}_{12}\text{H}_{11}\text{N}_5\text{O} \cdot \text{HCl}$: C, 51.90% H, 4.35% N, 25.22% and Found: C, 51.82% H, 4.43% N, 25.36%; 1,4-dihydro-2-methyl-4-oxo-6-[(2-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile: mp > 250 °C (cryst. from DMF-diethyl ether); NMR (DMSO- d_6) δ 2.15 (s, 3H), 4.68 (2H), 7.2 (2H), 7.7 (1H), 8.22 (1H), 8.47 (1H); Anal. Calcd for $\text{C}_{12}\text{H}_{11}\text{N}_5\text{O}$: C, 59.74% H, 4.60% N, 29.03% and Found: C, 59.69% H, 4.78% N, 28.83%; 1,4-dihydro-2-methyl-4-oxo-6-[(phenylmethyl)amino]-5-pyrimidinecarbonitrile: mp > 290 °C (cryst. from DMF); NMR (DMSO- d_6) δ 8.3 (t, 1H), 7.25 (s, 5H), 4.57 (d, 2H), 2.2 (s, 3H); Anal. Calcd for $\text{C}_{13}\text{H}_{12}\text{N}_4\text{O}$: C, 64.98% H, 5.04% N, 23.32% and Found: C, 64.84% H, 5.27% N, 23.28%; 1,4-dihydro-6-[(2-furanylmethyl)amino]-2-methyl-4-oxo-5-pyrimidinecarbonitrile: mp 297-300 °C (cryst. from methanol); NMR (DMSO- d_6) δ 2.2 (s, 3H), 4.55 (d, 2H), 6.25 (m, 2H), 7.5 (m, 1H), 8.2 (t, 1H), 11.4 (br, 1H); Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{N}_4\text{O}_2$: C, 57.38% H, 4.38% N, 24.34% and Found: C, 57.02% H, 4.49% N, 24.15%; 1,4-dihydro-2-methyl-6-[[2-(4-morpholinyl)ethyl]amino]-4-oxo-5-pyrimidinecarbonitrile: mp 227-230 °C (cryst. from methanol-acetonitrile); NMR (CDCl_3) δ 2.4 (s, 3H), 2.5 (m,

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6H), 3.65(m, 6H), 3.35(t, 1H); IR (mineral oil) 3340, 2850, 1670, 1595 cm^{-1} ; 6-[(cyclohexylmethyl)amino]-1,4-dihydro-2-methyl-4-oxo-5-pyrimidinecarbonitrile:m.p. 305-308°C; NMR(DMSO- d_6) of sodium salt δ 1.3(m), 1.98(s), 3.1(d, J=6.5);

5 Anal. Calcd for $\text{C}_{13}\text{H}_{18}\text{N}_4\text{O}$: C, 63.39% H, 7.36% N, 22.75% and Found: C, 63.56% H, 7.32% N, 22.64%; 1,4-dihydro-2-methyl-4-oxo-6-[[2-(3-thienyl)ethyl]amino]-5-pyrimidinecarbonitrile: mp 290-292°C; NMR (DMSO- d_6) δ 2.2 (s, 3H), 2.8 (t, 2H), 3.55 (m, 2H), 7.15 (m, 3H), 7.8 (t, 1H); Anal. Calcd for $\text{C}_{12}\text{H}_{12}\text{N}_4\text{OS}$: C, 55.36% H, 4.65% N, 21.52% and Found: C, 55.07% H, 4.61% N, 21.36%; 1,4-dihydro-6-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-methyl-4-oxo-5-pyrimidinecarbonitrile: mp 238-240°C (cryst. from methanol); NMR (DMSO- d_6) δ 2.2 (s, 3H), 2.7 (t, 2H), 3.5 (m, 2H), 3.7 (s, 3H), 3.73 (s, 3H), 6.75 (m, 3H), 7.7 (t, 1H); Anal. Calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_3$: C, 61.14% H, 5.77% N, 17.82% and Found: C, 60.63% H, 5.73% N, 17.68%; 1,4-dihydro-6-[[2-(1H-indol-3-yl)ethyl]amino]-2-methyl-4-oxo-5-pyrimidinecarbonitrile; mp 297-300°C (cryst. from methanol); NMR (DMSO- d_6) δ 2.2 (s, 3H), 2.9 (t, 2H), 3.6 (m, 2H), 7.1 (m, 4H), 7.85 (t, 1H), 10.75 (s, 1H), 11.5 (br, 1H); Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{N}_5\text{O}$: C, 65.51% H, 5.11% N, 23.88% and Found: C, 65.14% H, 5.21% N, 23.78%; 1,4-dihydro-2-methyl-4-oxo-6-[2-(3-pyridinyl)ethylamino]-5-pyrimidinecarbonitrile: mp > 250°C (cryst. from DMF); UV max (MeOH) 227 nm (ϵ 38,300), 263 (8000), 269 (8000), 290 (6800); NMR (DMSO- d_6) δ 2.2 (s, 3H), 2.85 (t, 2H), 3.6 (m, 2H), 7.25 (m, 1H), 7.6 (m, 1H), 7.85 (br, 1H), 8.4 (m, 2H); Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{N}_5\text{O}$: C, 61.16% H, 5.13% N, 27.43% and Found: C, 60.62% H, 5.12% N, 27.36%; 1,4-dihydro-2-methyl-4-oxo-6-[2-(4-pyridinyl)ethylamino]-5-pyrimidinecarbonitrile: mp > 250°C (cryst. from DMF); UV max (MeOH) 226 nm (ϵ 32,700), 257 (6370), 263 (6670), 289 (6870); NMR (DMSO- d_6) δ 2.2 (s, 3H), 2.82 (t, 2H), 3.6 (m, 2H), 7.18 (2d, 2H), 7.83 (br, 1H), 8.42 (2d, 2H), 11.5 (br, 1H); Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{N}_5\text{O}$: C, 61.15% H, 5.13% N, 27.43% and Found: C, 61.23% H, 5.20% N, 27.41%.

EXAMPLE 3

1,4-Dihydro-2-methyl-4-oxo-6-[(2-propenyl)amino]-5-pyrimidinecarbonitrile (I: $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{O}$, $\text{R}^3 = \text{CN}$, R^4 to $\text{R}^8 = \text{H}$, $m = 1$, $n = \text{O}$, and $\text{R}^9 = \text{ethenyl}$)

a) To a suspension of 2-cyano-3,3-bis(methylthio)-2-propenoic acid, methyl ester (8.12 g) in dimethoxyethane (13 mL) was added (2-propenyl)amine (2.51 g). The mixture dissolved. After about 15 min the solvent was evaporated

under nitrogen and the solid residue was filtered with diethyl ether to give 2-cyano-3-methylthio-3-(2-propenyl)amino-2-propenoic acid, methyl ester (8.61 g).

Similarly, but replacing (2-propenyl)amine with 3-aminopyridine, the following compound of formula VI was obtained; 2-cyano-3-methylthio-3-(3-pyridinyl)amino-2-propenoic acid, methyl ester: mp 93-94° C.

b) To a suspension of acetamidine hydrochloride (1.25 g, 1.1 eq) in DMF (45 mL) was added 2-cyano-3-methylthio-3-(2-propenyl)amino-2-propenoic acid, methyl ester (12.54 g, 1 eq) and potassium carbonate (1.82 g, 2.2 eq). The mixture was heated to 130° C for 22 hr, cooled in an ice water bath and diluted with water (20 mL). The precipitate was collected (0.7 g). The filtrate was evaporated and suspended in a small amount of water (7 mL) and filtered to give more product (0.3 g). The product was crystallized from DMF to yield the title compound (0.44 g): mp > 260° C; UV max (MeOH) 289 nm (ϵ 6610), 269 (5640), 227 (42640); NMR (DMSO- d_6) δ 2.2 (s, 3H), 3.95 (m, 2H), 5.05 (m, 2H), 5.8 (m, 1H), 7.9 (t, 1H); Anal. Calcd for $C_9H_{10}N_4O$: C, 56.84% H, 5.26% N, 29.47% and Found: C, 56.58% H, 5.34% N, 29.56%.

c) Similarly, replacement of 2-cyano-3-methylthio-3-(2-propenyl)-amino-2-propenoic acid, methyl ester with 2-cyano-3-methylthio-3-(3-pyridinyl)-amino-2-propenoic acid, methyl ester, the following compound of formula I was obtained: 1,4-dihydro-2-methyl-4-oxo-6-[(3-pyridinyl)amino]-5-pyrimidine-carbonitrile: mp > 260° C (cryst. from DMF); IR (mineral oil) 3320, 2700, 2210, 1695 cm^{-1} ; NMR (DMSO- d_6) δ 2.2 (s, 3H), 7.9 (m, 4H), 9.75 (br, 2H); Anal. Calcd for $C_{11}H_9N_5O$: C, 58.09% H, 3.99% N, 30.82% and Found: C, 57.80% H, 4.18% N, 30.36%.

EXAMPLE 4

4-Amino-2-methyl-6-[(3-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile (I: $R^1 = Me$, $R^2 = NH$, $R^3 = CN$, R^4 to $R^8 = H$, $m = 1$, $n = O$ and $R^9 = 3$ -pyridinyl)

a) To phosphorous oxychloride (42.9 g, or 26.1 mL, 8 eq) preheated to 100° C (bath temp.) was added, the sodium salt of 1,4-dihydro-2-methyl-4-oxo-6-[(3-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile (described in Example 2), (9.2 g, 1 eq). The reaction mixture was heated for 2 hr. The solution was cooled and poured into ice water (900 mL) with stirring. The

resulting solution was basified with sodium hydroxide (50%, 100 mL). Some ethyl acetate was added, and the resulting precipitate was filtered and dried to yield a solid (4.7 g). The aqueous filtrate was extracted with ethyl acetate, and the extract was dried and evaporated to give a residue (1.8 g). The combined material was crystallized from chloroform-hexane to give 4-chloro-2-methyl-6-[(3-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile: mp 165-167° C; UV max (MeOH) 305 nm (ϵ 4130), 254 (18100).

b) A solution of the latter compound (1.5 g, 1 eq) in methanol (25 mL) was cooled in an ice bath. Ammonia was passed into the solution for 20 min. The reaction mixture turned yellow. The mixture was heated in a closed container to 60° C for 2 hr. The precipitate began to appear concomitantly with discoloration. The mixture was stirred at room temperature overnight. The solvent was removed, water was added, and the solid was filtered to give crude product (1.4 g). Three crystallizations from DMF yielded the title compound (0.3 g): mp > 280° C; UV max (MeOH) 254 nm (ϵ 12740), 234 (44070); Anal. Calcd for $C_{12}H_{12}N_6$: C, 59.98% H, 5.04% N, 34.98% and Found: C, 59.50% H, 5.13% N, 34.41%.

EXAMPLE 5

1,4-Dihydro-2-methyl-6-[(3-pyridinylmethyl)amino]-4-thioxo-5-pyrimidinecarbonitrile (I: $R^1 = \text{Me}$, $R^2 = \text{S}$, $R^3 = \text{CN}$, R^4 to $R^8 = \text{H}$, $m = 1$, $n = \text{O}$, and $R^9 =$ 3-pyridinyl)

To ethanol (5 mL) was added a solution of potassium hydroxide (1.5 mL, 4 molar in water-ethanol 1:9). The mixture was cooled in ice-bath. Hydrogen sulphide was passed through the solution for 15 min. 4-Chloro-2-methyl-6-[(3-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile (described in Example 4, 0.78 g, 1 eq) in ethanol (7 mL) was added to the solution. The mixture was stirred at room temperature for 2.5 hr. Another portion of potassium hydroxide solution (1.5 mL) in ethanol (3.5 mL) was added. Hydrogen sulfide passed through for 15 min. It was stirred overnight at room temperature. The mixture was filtered and the precipitate was washed with some ethanol, to yield crude product (0.7 g). The solid was crystallized twice from DMF to yield the title compound (0.25 g): mp 310-312° C; NMR ($\text{DMSO}-d_6$) δ

13.2 (br, 1H), 8.8 (br, 1H), 8.5 (m, 2H), 7.5 (m, 2H), 4.6 (d, 2H), 2.3 (s, 3H);
Anal. Calcd for $C_{12}H_{11}N_5S$: C, 56.01% H, 4.31% N, 27.22% and Found: C,
55.48% H, 4.49% N, 26.68%.

EXAMPLE 6

1,4-Dihydro-2-methyl-4-oxo-6-[(3-pyridinylmethyl)amino]-5-pyrimidinecar-
boxamide (I: $R^1 = \text{Me}$, $R^2 = \text{O}$, $R^3 = \text{aminocarbonyl}$, R^4 to $R^8 = \text{H}$, $m = 1$,
5 $n = \text{O}$, and $R^9 = 3\text{-pyridinyl}$)

Sulfuric acid (4 mL) was added to 1,4-dihydro-2-methyl-4-oxo-
6-[(3-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile (1.2 g, described in
Example 2). The mixture was heated to 70° C for 4 hr. The reaction was
10 cooled to room temperature, and carefully poured on crushed ice (75 mL).
The resulting solution was neutralized with sodium hydroxide (50%, aqueous,
12.5 mL) when precipitate appeared. Filtrate after removal of precipitate
showed the pH to be 4.5-5.0. Eight more drops of sodium hydroxide were
added. More precipitate appeared. This was filtered off. The pH was checked
15 and found to be 5. One more drop changed the pH to 8. The combined solid
was dried and crystallized from boiling DMF to yield the title compound
(1.1 g): mp 264-266°; Anal. Calcd for $C_{12}H_{14}N_5O_2$: C, 55.38% H, 5.38% N,
26.9% and Found: C, 55.26% H, 5.12% N, 26.70%; IR (mineral oil) 3760, 3000,
1645, 1585 cm^{-1} ; NMR (DMSO- d_6) δ 8.5 (1H, m), 7.55 (1H, m), 7.25 (1H, m),
20 9.15 (1H, m), 4.7 (2H, d), 2.22 (3H, s).

EXAMPLE 7

2-Methylpropanimidamide (II: $R^1 = 1\text{-methylethyl}$)

Anhydrous hydrogen chloride was passed into a solution of 2-
methylpropanenitrile (30.4 g, 40 mL) in anhydrous ethanol (25 mL) until
25 saturation at 25° C. The stoppered reaction mixture did not crystallize
after 3 days and was evaporated to dryness under reduced pressure. The
oily residue crystallized after a while and was treated with a 10% solution
of anhydrous ammonia in ethanol (130 mL). After stirring for 3 hr, ammonium
chloride was filtered off, and the filtrate was concentrated until crystalline.
30 The first batch of the product (24.7 g) was collected by filtration, the second
batch (9.6 g) was obtained on further concentration of the filtrate to give
a total yield of the hydrochloride salt of the title compound (34.3 g): mp
155-157° C.

Similarly, by replacing 2-methylpropanenitrile with propanenitrile, 2,2-dimethylpropanenitrile, cyclopropyl nitrile, or 2-phenylethanenitrile, the following compounds of formula II were obtained respectively: propanimidamide hydrochloride (mp 130-132° C), 2,2-dimethylpropanimidamide hydrochloride (mp 186-188° C), cyclopropylmethanimidamide hydrochloride (mp 123-125° C), and 2-phenylethanimidamide hydrochloride (mp 145-147° C).

EXAMPLE 8

1,4-Dihydro-2-(1-methylethyl)-6-(methylthio)-4-oxo-5-pyrimidinecarbonitrile (IV: R¹ = 1-methylethyl)

a) A solution of 2-methylpropanimidamide hydrochloride (7.0 g, described in Example 7) in dimethylformamide (15 mL) was added dropwise to a suspension of sodium hydride (3.0 g, 50% in mineral oil, prewashed with hexane) in dimethylformamide (15 mL) and the whole mixture was left at 25° C for 1 hr. 2-Cyano-3,3-bis(methylthio)-2-propenoic acid, methyl ester (6.5 g) in dimethylformamide (15 mL) was then added dropwise, and the reaction mixture was stirred for an additional 4 hr at 25° C. Water (25 mL) was then added, and acidification with concentrated hydrochloric acid (10 mL) precipitated the product. The precipitate was collected and air dried to give the title compound (6.0 g): mp > 260° C.

b) → e) Similarly, by replacing 2-methylpropanimidamide with another compound of formula described in Example 7, the following compounds of formula IV were obtained respectively: 1,4-dihydro-2-ethyl-6-(methylthio)-4-oxo-5-pyrimidinecarbonitrile (mp > 260° C), 1,4-dihydro-2-(1,1-dimethylethyl)-6-(methylthio)-4-oxo-5-pyrimidinecarbonitrile (mp > 360° C), 2-cyclopropyl-1,4-dihydro-6-(methylthio)-4-oxo-5-pyrimidinecarbonitrile [NMR (DMSO-d₆) δ 1.2 (d, 4H), 2.0 (m, 1H), 2.5 (s, 3H)], and 1,4-dihydro-6-(methylthio)-4-oxo-2-(phenylmethyl)-5-pyrimidinecarbonitrile [NMR (DMSO-d₆) δ 2.6 (s, 3H), 4.0 (s, 2H), 7.4 (s, 5H)].

EXAMPLE 9

1,4-Dihydro-2-(1-methylethyl)-4-oxo-6-[(3-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile (I: R¹ = 1-methylethyl, R² = O, R³ = CN, R⁴ to R⁸ = H, m = 1, n = O, and R⁹ = 3-pyridinyl)

- a) 3-(Aminomethyl)pyridine (16 mL) was added to 1,4-dihydro-2-(1-methylethyl)-6-(methylthio)-4-oxo-5-pyrimidinecarbonitrile (6 g, described in Example 8) in 1,2-dimethoxyethane (50 mL), and the mixture was refluxed overnight. Evaporation to dryness under reduced pressure gave the crude product which was chromatographed over silica acid with chloroform-methanol (97:3). The product was isolated as a colorless solid which was crystallized from methanol-water to give the title compound (3.4 g): mp $> 260^{\circ}\text{C}$; NMR (DMSO- d_6) δ 1.1 (d, 6H), 2.7 (m, 1H), 4.55 (m, 2H), 7.3-8.4 (m, 4H), 11.5 (br, 2H); IR (mineral oil) 3335, 2900, 2210, 1660, 1585 cm^{-1} ; Anal. Calcd for $\text{C}_{14}\text{H}_{15}\text{N}_5\text{O}$: C, 62.44% H, 5.61% N, 25.94% and Found: C, 62.12% H, 5.63% N, 25.92%.
- b) to e) Similarly, by replacing 1,4-dihydro-2-(1-methylethyl)-6-(methylthio)-4-oxo-5-pyrimidinecarbonitrile with another compound of formula IV described in Example 8, the following compounds of formula I were obtained respectively:
- 1,4-dihydro-2-ethyl-4-oxo-6-[(3-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile hydrochloride: mp $> 265^{\circ}\text{C}$ (cryst. from methanol-water); NMR (DMSO- d_6) 1.05 (t, 3H), 2.45 (d, 2H), 4.75 (d, 2H), 6.2 (br, 2H), 8.4 (m, 4H), 11.4 (br, 1H); IR (mineral oil) 3280, 2600, 2220, 2080, 1960, 1650 cm^{-1} ; Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{ClN}_5\text{O}$: C, 53.52% H, 4.84% N, 24.00% and Found: C, 53.17% H, 4.84% N, 23.74%; 1,4-dihydro-2-(1,1-dimethylethyl)-4-oxo-6-[(3-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile hydrochloride: mp $> 260^{\circ}\text{C}$ (cryst. from methanol-water); NMR (DMSO- d_6) δ 1.17 (s, 9H), 4.15 (d, 2H), 8.5 (m, 4H), 8.6 (br, 1H), 8.9 (br, 1H), 11.9 (s, 1H); IR (mineral oil) 3280, 3180, 3100, 2600, 2220, 2100, 1970, 1660 cm^{-1} ; Anal. Calcd for $\text{C}_{18}\text{H}_{17}\text{N}_5\text{O}$: C, 56.34% H, 5.67% N, 21.90% and Found: C, 57.74% H, 5.61% N, 21.96%; 2-cyclopropyl-1,4-dihydro-4-oxo-6-[(3-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile: mp $> 260^{\circ}\text{C}$ (cryst. from 1,2-dimethoxyethane); NMR (DMSO- d_6) δ 1.0 (m, 4H), 1.8 (m, 1H), 4.5 (d, 2H), 7.5-8.5 (m, 4H), 12.4 (br, 1H); IR (mineral oil) 3300, 2850, 2190, 1685 cm^{-1} ; Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{N}_5\text{O}$: C, 62.91% H, 4.90% N, 26.20% and Found: C, 62.31% H, 4.90% N, 25.98%; and 1,4-dihydro-4-oxo-2-(phenylmethyl)-6-[(3-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile: mp $> 260^{\circ}\text{C}$ (cryst. from acetonitrile); NMR (DMSO- d_6) δ 3.8 (s, 2H), 4.5 (d, 2H), 7.25

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(s, 5H), 7.45 and 8.4 (m, 4H), 8.4 (br, 1H); IR (mineral oil) 3330, 2800, 2210, 1660, 1590 cm^{-1} ; Anal. Calcd for $\text{C}_{18}\text{H}_{15}\text{N}_5\text{O}$: C, 68.13% H, 4.76% N, 22.07% and Found: C, 67.83% H, 4.82% N, 21.85%.

EXAMPLE 10

5 1,4-Dihydro-6-(ethylamino)-2-methyl-4-oxo-5-pyrimidinecarbonitrile (1: $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{O}$, $\text{R}^3 = \text{H}$ and $\text{R}^4 = \text{Et}$)

a) To a suspension of 2-cyano-3,3-bis(methylthio)-2-propenoic acid, methyl ester (8.12 g, 1 eq) in dimethoxyethane (14 mL) was added a solution of ethylamine (2.16 g, 1.2 eq.) in dimethoxyethane (6.5 mL). The suspension turned
10 to solution, and a white solid began to precipitate. After about 10 min the solvent was removed and the residue was filtered with diethyl ether to yield 2-cyano-3-ethylamino-3-methylthio-2-propenoic acid, methyl ester (7.2 g): mp 86-88°C.

b) To a solution of acetamidine hydrochloride (0.83 g, 1.1 eq) in DMF (5.5
15 mL) was added potassium carbonate (1.22 g, 2.2 eq) and the mixture was stirred at room temperature for about 10 min. The above cyanoester (1.6 g, 1 eq) was added and the mixture was heated to 90°C overnight. The reaction mixture was cooled, diluted with water and filtered to give a solid (0.3 g). Further concentration to dryness followed by filtration of residue with small amount of
20 water gave more solid (0.8 g). The two solids were pooled and crystallized from methanol to give the title compound (0.6 g): mp > 290°C; Anal. Calcd. for $\text{C}_8\text{H}_{10}\text{N}_4\text{O}$: C, 53.93% H, 5.61% N, 31.46% and Found: C, 53.67% H, 5.83% N, 31.31%; IR (mineral oil) 3300, 2800, 2220, 1650 cm^{-1} ; $\text{UV}\lambda_{\text{max}}$ (MeOH) 289 nm (ϵ 6140), 268 (5240), 226 (40,100); NMR ($\text{DMSO}-d_6$) δ 7.75 (t, 1H), 3.4 (m, 2H),
25 2.23 (s, 3H), 1.1 (s, 3H).

c) to f) Similarly, the following compounds of formula I can be prepared: 1,4-dihydro-6-(butylamino)-2-cyclohexyl-4-oxo-5-pyrimidinecarbonitrile, 1,4-dihydro-6-(diethylamino)-2-butyl-4-oxo-5-pyrimidinecarbonitrile, 1,4-dihydro-6-(N-methyl-N-propylamino)-2-benzyl-4-oxo-5-pyrimidinecarbonitrile, and 1,4-
30 dihydro-6-(propylamino)-2-cyclopropyl-4-oxo-5-pyrimidinecarbonitrile.

EXAMPLE 11

Test for Cardiotonic Activity in Isolated Cat Papillary Muscle

A cat of either sex was anesthetized with Na pentobarbital, 25-30 mg/kg i.v. The heart was rapidly removed and placed in cool Tyrode's solution 5 which had been equilibrated with 95% O₂-5% CO₂. The right ventricle was opened by cutting down the sides and around the apex so that the free wall could be folded back on the atrioventricular groove. Usually at least three suitably-sized papillary muscles were found (1 mm or less in thickness). Threads were tied around the chordae tendoneae and the base of the muscle just above its point 10 of insertion into the ventricular wall. The chordae were cut, and the muscle was removed along with a small button of ventricular wall. If a sufficient number of papillary muscles were not present, trabeculae carneae could also be used. The best ones were usually found inserting just under the valve.

The preparations were mounted in tissue baths containing Tyrode's 15 solution at 37°C bubbled with 95% O₂-5% CO₂. One thread was affixed to a tissue holder incorporating a pair of platinum electrodes and the other thread was attached to a force displacement transducer. Initial tension placed on the preparation was 0.2 g (less for very small muscles). The preparations were stimulated with square-wave pulses, 2-4 msec. in duration and 10% above 20 threshold voltage, at a rate of 0.5Hz. The muscles were then gently and gradually stretched to their optimum force-length relation (at which twitch tension was maximal-further stretching did not result in any further increase in the overall magnitude of the twitch). The preparations were then allowed to 25 equilibrate for one hour with frequent changes of the bathing fluid (10-15 min intervals). The test compound was added to the bath in 0.1 mL of vehicle and incubated with the preparation for 15 min or until peak effect was attained.

Using this method, the following representative compounds of formula I were effective for increasing the force of contraction of the papillary muscle (the amount of test compound in the bath and increase in contractility is given in 30 the parenthesis): 1,4-dihydro-2-methyl-4-oxo-6-[(3-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile (at 10⁻⁴ molar increased contractility by 98%), 1,4-dihydro-2-methyl-4-oxo-6-[(4-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile

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(at 10^{-4} molar increased contractility by 139%), 1,4-dihydro-2-methyl-4-oxo-6-[(phenylethyl)amino]-5-pyrimidinecarbonitrile (at 10^{-4} molar increased contractility by 142%), 1,4-dihydro-2-ethyl-4-oxo-6-[(3-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile (at 10^{-4} molar increased contractility by 140%), 1,4-dihydro-6-[(2-furanylmethyl)amino]-2-methyl-4-oxo-5-pyrimidinecarbonitrile (at 10^{-4} molar increased contractility by 108%), 2-cyclopropyl-1,4-dihydro-4-oxo-6-[(3-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile (at 10^{-4} molar increased contractility by 129%), 1,4-dihydro-2-methyl-6-[(2-(4-morpholinyl)ethyl)amino]-4-oxo-5-pyrimidinecarbonitrile (at 10^{-4} molar increased contractility by 62%), 1,4-dihydro-2-methyl-4-oxo-6-[[2-(3-thienyl)ethyl]amino]-5-pyrimidinecarbonitrile (at 10^{-4} molar increased contractility by 149%), 1,4-dihydro-2-methyl-4-oxo-6-[(2-propenyl)amino]-5-pyrimidinecarbonitrile (at 10^{-4} molar increased contractility by 61%) and 1,4-dihydro-6-(ethylamino)-2-methyl-4-oxo-5-pyrimidinecarbonitrile (at 10^{-4} molar increased contractility by 88%).

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EXAMPLE 12

Pentobarbital-induced Cardiac Failure in the Dog

A dog of either sex was anesthetized with Na pentobarbital, 30-35 mg/kg i.v. The trachea was intubated and the animal was respired at a rate of 20 breaths/min (stroke volume = 15 cc/kg). Both femoral veins were cannulated. One cannula was used for infusion of pentobarbital to induce and maintain failure, the other for injection of test compounds. A cannula was inserted into the aorta via a femoral artery and the cannula was attached to a blood pressure transducer for measurement of systolic, diastolic and mean aortic blood pressure. A Millar pressure-tip catheter was inserted into the other femoral artery and advanced into the left ventricle to record intraventricular pressure and dP/dt . Subdermal needle electrodes were used to record a lead II electrocardiogram and heart rate.

Following a stabilization period of at least 30 min, experimental failure was induced by the i.v. infusion of Na pentobarbital, 0.75 mg/kg/min in 0.2 mL of saline/min, until a 40-50% decrease in peak positive dP/dt was obtained. The failure state was maintained at this level throughout the experiment by continuous infusion of Na pentobarbital, 0.11-0.15 mg/kg/min. Once the maintenance infusion was started, at least 15 min were allowed to elapse before test drugs were administered.

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Test compounds were prepared in N saline. Increasingly higher doses were given i.v. at 30 min-1hr intervals in order to determine a therapeutic (50% increase in dP/dt) to toxic (appearance of arrhythmias) ratio where possible.

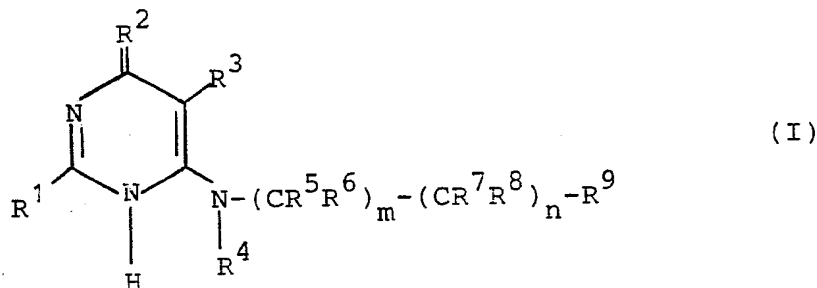
Using this method, the following representative compounds of formula I were effective for increasing the cardiac contractility of the heart (the amount of test compound in mg per kg of body weight administered i.v. to give a 50% increase in dP/dt is given in the parenthesis): 1,4-dihydro-2-methyl-4-oxo-6-[(3-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile (0.06 mg/kg), 1,4-dihydro-2-methyl-4-oxo-6-[(4-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile (0.07 mg/kg), 1,4-dihydro-2-ethyl-4-oxo-6-[(3-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile (0.05 mg/kg), 1,4-dihydro-6-[(2-furanylmethyl)amino]-2-methyl-4-oxo-5-pyrimidinecarbonitrile (0.06 mg/kg), 2-cyclopropyl-1,4-dihydro-4-oxo-6-[(3-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile (0.02 mg/kg), 1,4-dihydro-2-methyl-4-oxo-6-[[2-(3-thienyl)ethyl]amino]-5-pyrimidinecarbonitrile (0.08 mg/kg), and 1,4-dihydro-6-(ethylamino)-2-methyl-4-oxo-5-pyrimidinecarbonitrile (0.02 mg/kg).

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CLAIMS

1. A compound of the formula I



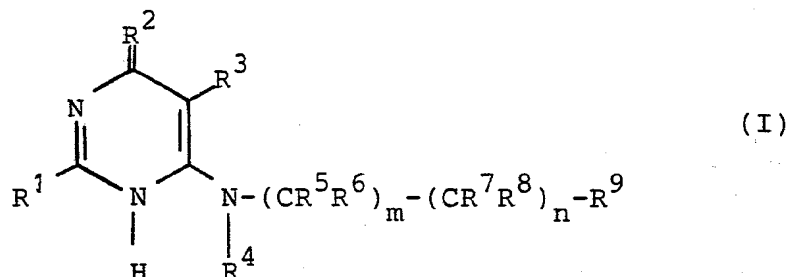
in which R¹ is lower alkyl, cyclo(lower)alkyl, phenyl (lower)alkyl, or trifluoromethyl; R² is oxo, thioxo or imino; R³ is cyano, aminocarbonyl, nitro, methylsulfonyl or aminosulfonyl; R⁴, R⁵, R⁶, R⁷ and R⁸ each independently is hydrogen or lower alkyl; R⁹ is hydrogen, lower alkenyl, 1-piperidinyl, 1-pyrrolidinyl, 1-piperazinyl, lower alkynyl, cyclo(lower)alkyl, 2,3 or 4-pyridinyl, 2 or 3-furanyl, 2 or 3-indolyl, 2 or 3-thienyl, 5-imidazolyl, 4-morpholinyl, phenyl, phenyl mono- or disubstituted with hydroxy or lower alkoxy, 4-thiomorpholinyl, pyrazinyl, pyridazinyl, triazinyl, pyrrolyl, pyrazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, isoxazolyl, furazolyl, oxathiazolyl, quinolinyl, isoquinolinyl, pyridopyrimidinyl, benzoxazolyl, benzimidazolyl, benzthiazolyl, benzoxazinyl, benzpyronyl, isoindolyl, or indolazinyl; and m and n each independently is an integer 0 to 2; or a therapeutically acceptable addition salt thereof for use as a pharmaceutical.

2. A pharmaceutical composition comprising a compound of formula I as defined in Claim 1 or a therapeutically acceptable addition salt thereof and a pharmaceutically acceptable carrier.

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3. A cardiotonic pharmaceutical composition,
which comprises a compound of the formula I



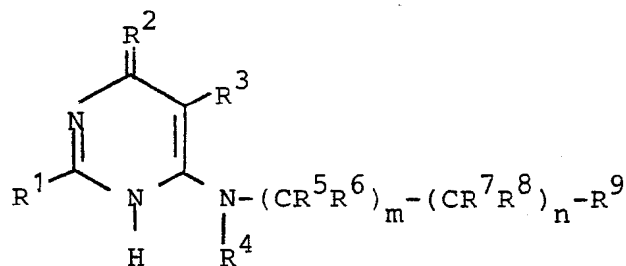
in which R^1 is lower alkyl, cyclo(lower)alkyl, phenyl(lower)-alkyl, or trifluoromethyl; R^2 is oxo, thioxo or imino; R^3 is cyano, aminocarbonyl, nitro, methylsulfonyl or aminosulfonyl; R^4 , R^5 , R^6 , R^7 and R^8 each independently is hydrogen or lower alkyl; R^9 is hydrogen, lower alkenyl, 1-piperidinyl, 1-pyrrolidinyl, 1-piperazinyl, lower alkynyl, cyclo(lower)alkyl, 2,3 or 4-pyridinyl, 2 or 3-furanyl, 2 or 3-indolyl, 2 or 3-thienyl, 5-imidazolyl, 4-morpholinyl, phenyl, phenyl mono- or disubstituted with hydroxy or lower alkoxy, 4-thiomorpholinyl, pyrazinyl, pyridazinyl, triazinyl, pyrrolyl, pyrazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, isoxazolyl, furazolyl, oxathiazolyl, quinolinyl, isoquinolinyl, pyridopyrimidinyl, benzoxazolyl, benzimidazolyl, benzthiazolyl, benzoxazinyl, benzpyrrolyl, isoindolyl, or indolazinyl; and m and n each independently is an integer 0 to 2; or a therapeutically acceptable salt thereof and an agent commonly used in treatment of congestive heart failure.

4. A cardiotonic pharmaceutical composition as claimed in claim 3 wherein said agent is selected from isosorbide dinitrate, captopril, nifedipine, hydralazine, prazosin, hydrochlorothiazide, furosemide, spironolactone, digitalis and dobutamine.

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5. A compound of the formula I



in which R¹ is lower alkyl, cyclo(lower)alkyl, phenyl-(lower)alkyl, or trifluoromethyl; R² is oxo, thioxo or imino; R³ is cyano, aminocarbonyl, nitro, methylsulfonyl or aminosulfonyl; R⁴, R⁵, R⁶, R⁷ and R⁸ each independently is hydrogen or lower alkyl; R⁹ is hydrogen, lower alkenyl, 1-piperidinyl, 1-pyrrolidinyl, 1-piperazinyl, lower alkynyl, cyclo(lower)alkyl, 2,3 or 4-pyridinyl, 2 or 3-furanyl, 2 or 3-indolyl, 2 or 3-thienyl, 5-imidazolyl, 4-morpholinyl, phenyl, phenyl mono- or disubstituted with hydroxy or lower alkoxy, 4-thiomorpholinyl, pyrazinyl, pyridazinyl, triazinyl, pyrrolyl, pyrazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, isoxazolyl, furazolyl, oxathiazolyl, quinolinyl, isoquinolinyl, pyridopyrimidinyl, benzoxazolyl, benzimidazolyl, benzthiazolyl, benzoxazinyl, benzpyronyl, isoindolyl, or indolazinyl; and m and n each independently is an integer 0 to 2; or a therapeutically acceptable addition salt thereof; with the proviso that when R¹ is lower alkyl, cyclo(lower)alkyl or benzyl; R² is oxo or thioxo, R³ is cyano, R⁴ is lower alkyl and m and n are each 0, then R⁹ is other than hydrogen.

6. A compound as claimed in Claim 5 wherein R¹ is lower alkyl, cyclo(lower)alkyl or benzyl; R² is oxo, thioxo or imino; R³ is cyano or aminocarbonyl; R⁴, R⁶ and R⁸ each independently is hydrogen or lower alkyl; R⁵ and R⁷ are hydrogen; R⁹ is lower alkenyl, cyclo(lower)alkyl, 2,3 or 4-pyridinyl, 2 or 3-furanyl,

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2 or 3-indolyl, 2 or 3-thienyl, 4-morpholinyl, phenyl or phenyl mono or disubstituted with hydroxy or lower alkoxy; and m and n each independently is an integer 0 to 2; or a therapeutically acceptable addition salt thereof.

7. A compound as claimed in Claim 5 wherein R¹ is lower alkyl, cyclo(lower)alkyl or benzyl; R² is oxo or thioxo, R³ is cyano; R⁴, R⁵ and R⁷ are hydrogen; R⁶ and R⁸ each independently is hydrogen or lower alkyl; R⁹ is lower alkenyl, 2,3 or 4-pyridinyl, 2-furanyl, 3-indolyl, 3-thienyl, 4-morpholinyl, phenyl or phenyl mono- or disubstituted with lower alkoxy; and m and n each independently is the integer 0 or 1; or a therapeutically acceptable addition salt thereof.

8. A compound as claimed in Claim 5 which is 1,4-dihydro-2-methyl-4-oxo-6-[(3-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile; 1,4-dihydro-2-methyl-6-[N-methyl-N-(3-pyridinylmethyl)amino]-4-oxo-5-pyrimidinecarbonitrile; 1,4-dihydro-2-methyl-4-oxo-6-[(phenylethyl)amino]-5-pyrimidinecarbonitrile; 1,4-dihydro-2-methyl-4-oxo-6-[(2-pyridinylethyl)amino]-5-pyrimidinecarbonitrile; 1,4-dihydro-2-methyl-4-oxo-6-[(4-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile; 1,4-dihydro-2-methyl-4-oxo-6-[(2-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile; 1,4-dihydro-2-methyl-4-oxo-6-[(phenylmethyl)amino]-5-pyrimidinecarbonitrile; 1,4-dihydro-2-methyl-4-oxo-6-[2-(3-pyridinyl)ethylamino]-5-pyrimidinecarbonitrile; 1,4-dihydro-2-methyl-4-oxo-6-[2-(4-pyridinyl)ethylamino]-5-pyrimidinecarbonitrile; 1,4-dihydro-2-methyl-4-oxo-6-[(3-pyridinyl)amino]-5-pyrimidinecarbonitrile; 1,4-dihydro-2-methyl-6-[(3-pyridinylmethyl)amino]-4-thioxo-5-pyrimidinecarbonitrile; 1,4-dihydro-2-ethyl-4-oxo-6-[(3-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile; 1,4-dihydro-2-(1-methylethyl)-4-oxo-6-[(3-pyridinylmethyl)-

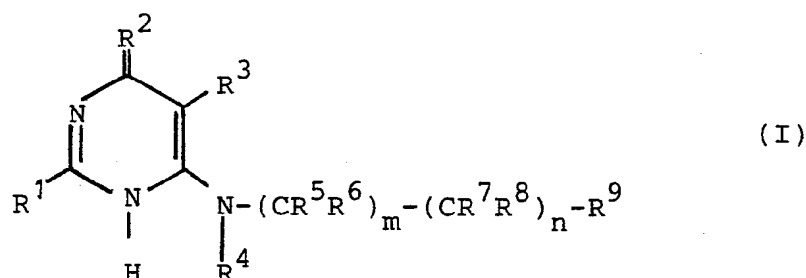
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amino]-5-pyrimidine-carbonitrile; 2-cyclopropyl-1,4-dihydro-4-oxo-6-[(3-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile; 1,4-dihydro-2-(1,1-dimethylethyl)-4-oxo-6-[(3-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile; 1,4-dihydro-4-oxo-2-phenylmethyl-6-[(3-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile; or a pharmaceutically acceptable salt thereof.

9. A compound as claimed in Claim 5 which is 1,4-dihydro-6-[(2-furanylmethyl)amino]-2-methyl-4-oxo-5-pyrimidinecarbonitrile; 1,4-dihydro-2-methyl-6-[[2-(4-morpholinyl)ethyl]amino]-4-oxo-5-pyrimidinecarbonitrile; 1,4-dihydro-2-methyl-4-oxo-6-[[2-(3-thienyl)ethyl]amino]-5-pyrimidinecarbonitrile; 1,4-dihydro-6-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-methyl-4-oxo-5-pyrimidine-carbonitrile; 1,4-dihydro-6-[[2-(1H-indol-3-yl)ethyl]amino]-2-methyl-4-oxo-5-pyrimidinecarbonitrile; 1,4-dihydro-2-methyl-4-oxo-6-[(2-propenyl)amino]-5-pyrimidinecarbonitrile; or a pharmaceutically acceptable addition salt thereof.

10. A process for preparing a compound of formula I



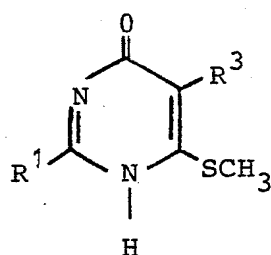
in which R¹ is lower alkyl, cyclo(lower)alkyl, phenyl-(lower)alkyl, or trifluoromethyl; R² is oxo, thioxo or imino; R³ is cyano, aminocarbonyl, nitro, methylsulfonyl or aminosulfonyl; R⁴, R⁵, R⁶, R⁷ and R⁸ each independently is hydrogen or lower alkyl; R⁹ is hydrogen,

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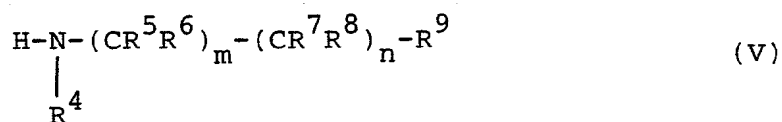
lower alkenyl, 1-piperidinyl, 1-pyrrolidinyl, 1-piperazinyl, lower alkynyl, cyclo(lower)alkyl, 2,3 or 4-pyridinyl, 2 or 3-furanyl, 2 or 3-indolyl, 2 or 3-thienyl, 5-imidazolyl, 4-morpholinyl, phenyl, phenyl mono- or disubstituted with hydroxy or lower alkoxy, 4-thiomorpholinyl, pyrazinyl, pyridazinyl, triazinyl, pyrrolyl, pyrazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, isoxazolyl, furazolyl, oxathiazolyl, quinolinyl, isoquinolinyl, pyridopyrimidinyl, benzoxazolyl, benzimidazolyl, benthiazolyl, benzoxazinyl, benzpyronyl, isoindolyl, or indolazinyl; and m and n each independently is an integer 0 to 2; or a therapeutically acceptable addition salt thereof which comprises:

(a) reacting a pyrimidine IV



(IV)

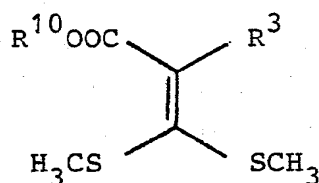
in which R¹ is as defined above and R³ is cyano, nitro, methylsulfonyl or aminosulfonyl with an amine V



(V)

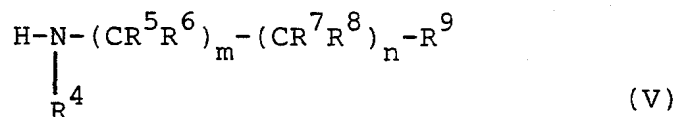
in which R⁴ to R⁹, m and n are as defined above to obtain the compound corresponding to formula I in which R² is oxo and R³ is cyano, nitro, methylsulfonyl or aminosulfonyl and R¹, R⁴ to R⁹, m and n are as defined above, or

(b) reacting a compound of formula III

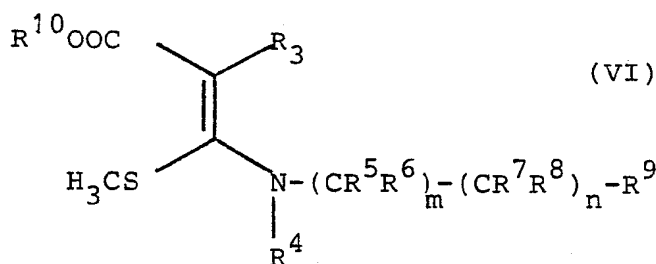


(III)

in which R^3 is cyano, nitro, methylsulfonyl or aminosulfonyl and R^{10} is lower alkyl with an amine V



in which R^4 to R^9 , m and n are as defined above to obtain the compound VI



in which R^3 is cyano, nitro, methylsulfonyl or aminosulfonyl and R^4 to R^{10} , m and n are as defined above, and condensing the compound VI with an amidine II

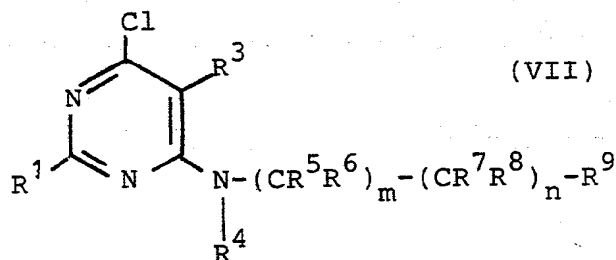


in which R^1 is as defined above to give a compound corresponding to formula I in which R^2 is oxo, R^3 is cyano, nitro, methylsulfonyl or aminosulfonyl and R^1 , R^4 to R^9 , m and n are as defined above,

(c) if desired converting a compound of formula I in which R^2 is oxo to a compound corresponding to formula I in which R^2 is thioxo by reacting a sodium salt of a compound of formula I in which R^2 is oxo with phosphorous oxychloride to obtain a 4-chloropyrimidine of formula VII

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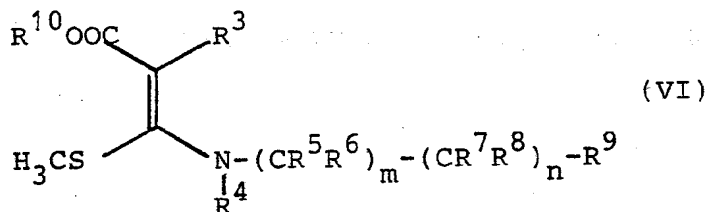
in which R^3 is cyano, nitro, methylsulfonyl or aminosulfonyl and R^1 , R^4 to R^9 , m and n are as defined above and treating the 4-chloropyrimidine VII with an aqueous ethanol solution of potassium hydroxide and hydrogen sulfide to obtain the compound corresponding to formula I in which R^2 is thioxo, R^3 is cyano, nitro, methylsulfonyl or aminosulfonyl and R^1 , R^4 to R^9 , m and n are as defined above,

(d) if desired, treating a 4-chloropyrimidine VII with a solution of an inert organic solvent containing an excess of ammonia to obtain the compound corresponding to formula I in which R^2 is imino, R^3 is cyano, nitro, methylsulfonyl or aminosulfonyl, and R^1 , R^4 to R^9 , m and n are as defined above

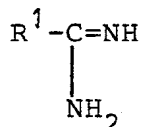
(e) if desired, hydrolyzing a compound of formula I in which R^3 is cyano; and R^1 , R^2 , R^4 to R^9 , m and n are as defined above, with sulfuric acid to obtain the compound corresponding to formula I in which R^3 is aminocarbonyl; and R^1 , R^2 , R^4 to R^9 , m and n are as defined above.

11. A process for preparing a compound of formula I as claimed in Claim 5 which comprises:

a) condensing a compound of formula VI



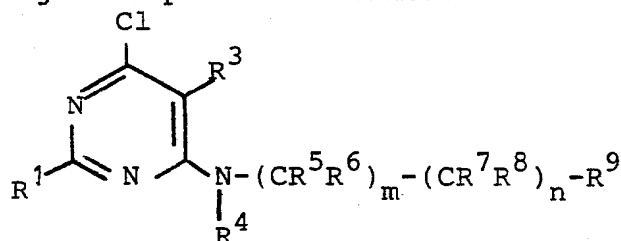
wherein R^3 is cyano, nitro, methylsulfonyl or amino-sulfonyl and R^4 to R^9 , m and n are as defined in Claim 5, and R^{10} is lower alkyl with an amidine of formula II



II

wherein R^1 is as defined in Claim 5 to give a compound of formula I wherein R^2 is oxo, R^3 is cyano, nitro methylsulfonyl or aminosulfonyl and R^1 , R^4 to R^9 , m and n are as defined in Claim 5, or

b) reacting a compound of formula VII



(VII)

wherein R^1 , R^4 to R^9 , m and n are as defined in Claim 5 and R^3 is cyano, nitro, methylsulfonyl or amino-sulfonyl, with an aqueous ethanol solution of potassium hydroxide and hydrogen sulfide to give a corresponding compound of formula I wherein X is thioxo, or

c) reacting a compound of formula VII as defined above with a solution of an inert organic solvent containing an excess of ammonia to give a corresponding compound of formula I wherein R^2 is imino, or

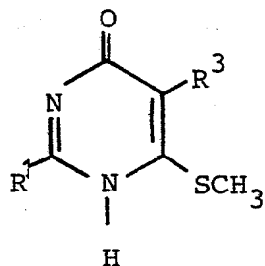
d) hydrolysing a compound of formula I as defined in Claim 5 wherein R^3 is cyano to give a compound of formula I wherein R^3 is aminocarbonyl or

e) converting a compound of formula I as defined in Claim 5 to a therapeutically acceptable salt thereof.

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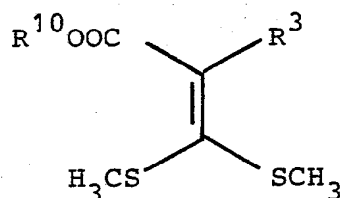
12. A compound of formula IV



(IV)

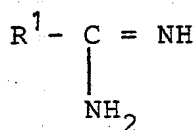
in which R^1 is lower alkyl, cyclo(lower)alkyl, phenyl (lower)alkyl or trifluoromethyl, and R^3 is cyano, nitro, methylsulfonyl or aminosulfonyl.

13. A process for preparing a compound of formula IV as claimed in Claim 1 which comprises condensing a compound of formula III



(III)

with a compound of formula II,



(II)

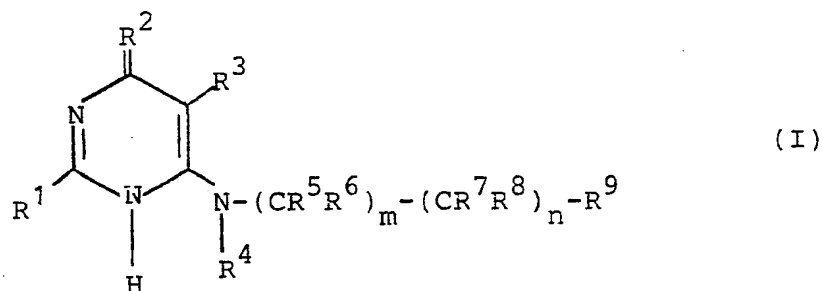
in which formulae R^1 and R^3 are as defined in Claim 12 and R^{10} represents lower alkyl.

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CLAIMS FOR AUSTRIA

1. A process for preparing a compound of the formula I



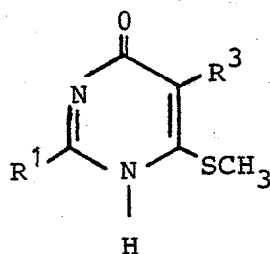
in which R^1 is lower alkyl, cyclo(lower)alkyl, phenyl (lower)alkyl, or trifluoromethyl; R^2 is oxo, thioxo or imino; R^3 is cyano, aminocarbonyl, nitro, methylsulfonyl or aminosulfonyl; R^4 , R^5 , R^6 , R^7 and R^8 each independently is hydrogen or lower alkyl; R^9 is hydrogen, lower alkenyl, 1-piperidinyl, 1-pyrrolidinyl, 1-piperazinyl, lower alkynyl, cyclo(lower)alkyl, 2,3 or 4-pyridinyl, 2 or 3-furanyl, 2 or 3-indolyl, 2 or 3-thienyl, 5-imidazolyl, 4-morpholinyl, phenyl, phenyl mono- or disubstituted with hydroxy or lower alkoxy, 4-thiomorpholinyl, pyrazinyl, pyridazinyl, triazinyl, pyrrolyl, pyrazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, isoxazolyl, furazolyl, oxathiazolyl, quinolinyl, isoquinolinyl, pyridopyrimidinyl, benzoxazolyl, benzimidazolyl, benzthiazolyl, benzoxazinyl, benzpyronyl, isoindolyl, or indolazinyl; and m and n each independently is an integer 0 to 2; or a therapeutically acceptable addition salt thereof,

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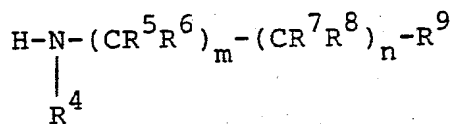
which comprises;

(a) reacting a pyrimidine IV



(IV)

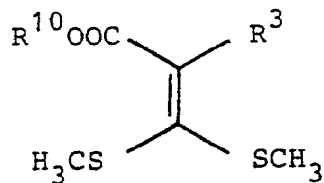
in which R^1 is as defined above and R^3 is cyano, nitro, methylsulfonyl or aminosulfonyl with an amine V



(V)

in which R^4 to R^9 , m and n are as defined above to obtain the compound corresponding to formula I in which R^2 is oxo and R^3 is cyano, nitro, methylsulfonyl or aminosulfonyl and R^1 , R^4 to R^9 , m and n are as defined above, or

(b) reacting a compound of formula III

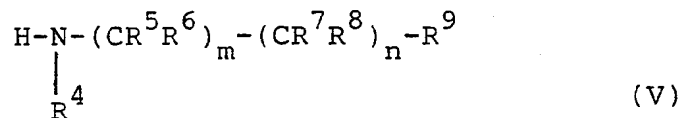


(III)

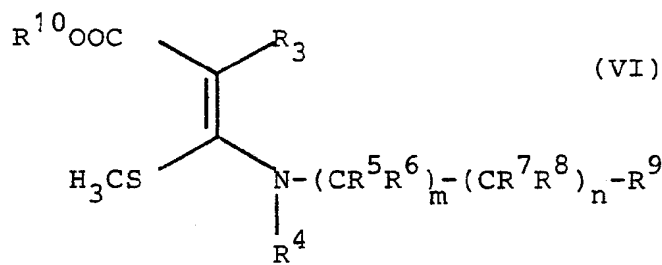
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in which R^3 is cyano, nitro, methylsulfonyl or amino-sulfonyl and R^{10} is lower alkyl with an amine V



in which R^4 to R^9 , m and n are as defined above to obtain the compound VI



in which R^3 is cyano, nitro, methylsulfonyl or amino-sulfonyl and R^4 to R^{10} , m and n are as defined above, and condensing the compound VI with an amidine II

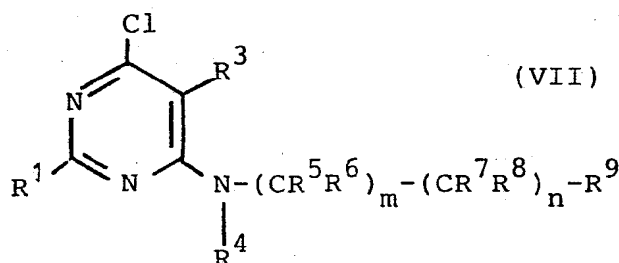


in which R^1 is as defined above to give a compound corresponding to formula I in which R^2 is oxo, R^3 is cyano, nitro, methylsulfonyl or aminosulfonyl and R^1 , R^4 to R^9 , m and n are as defined above,

(c) if desired converting a compound of formula I in which R^2 is oxo to a compound corresponding to formula I in which R^2 is thioxo by reacting a sodium salt of a compound of formula I in which R^2 is oxo with phosphorous oxychloride to obtain a 4-chloropyrimidine of formula VII

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in which R^3 is cyano, nitro, methylsulfonyl or aminosulfonyl and R^1 , R^4 to R^9 , m and n are as defined above and treating the 4-chloropyrimidine VII with an aqueous ethanol solution of potassium hydroxide and hydrogen sulfide to obtain the compound corresponding to formula I in which R^2 is thioxo, R^3 is cyano, nitro, methylsulfonyl or aminosulfonyl and R^1 , R^4 to R^9 , m and n are as defined above.

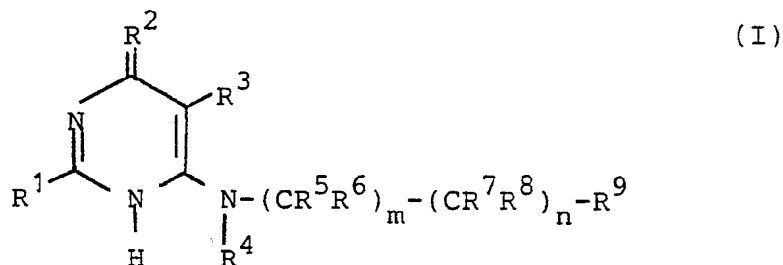
(d) if desired, treating a 4-chloropyrimidine VII with a solution of an inert organic solvent containing an excess of ammonia to obtain the compound corresponding to formula I in which R^2 is imino, R^3 is cyano, nitro, methylsulfonyl or aminosulfonyl, and R^1 , R^4 to R^9 , m and n are as defined above

(e) if desired, hydrolyzing a compound of formula I in which R^3 is cyano; and R^1 , R^2 , R^4 to R^9 , m and n are as defined above, with sulfuric acid to obtain the compound corresponding to formula I in which R^3 is aminocarbonyl; and R^1 , R^2 , R^4 to R^9 , m and n are as defined above.

2. A process for preparing a compound of formula I

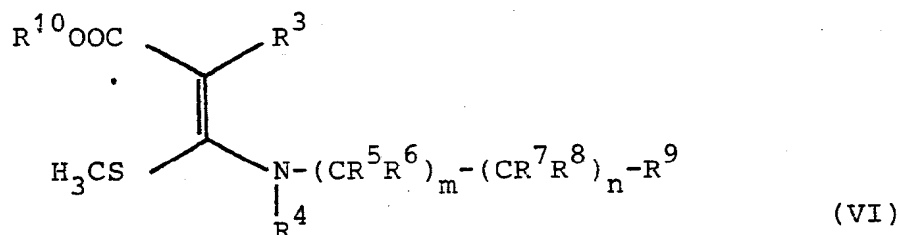
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in which R^1 is lower alkyl, cyclo(lower)alkyl, phenyl-(lower)alkyl, or trifluoromethyl; R^2 is oxo, thioxo or imino; R^3 is cyano, aminocarbonyl, nitro, methylsulfonyl or aminosulfonyl; $\text{R}^4, \text{R}^5, \text{R}^6, \text{R}^7$ and R^8 each independently is hydrogen or lower alkyl; R^9 is hydrogen, lower alkenyl, 1-piperidinyl, 1-pyrrolidinyl, 1-piperazinyl, lower alkynyl, cyclo(lower)alkyl, 2,3 or 4-pyridinyl, 2 or 3-furanyl, 2 or 3-indolyl, 2 or 3-thienyl, 5-imidazolyl, 4-morpholinyl, phenyl, phenyl mono- or disubstituted with hydroxy or lower alkoxy, 4-thiomorpholinyl, pyrazinyl, pyridazinyl, triazinyl, pyrrolyl, pyrazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, isoxazolyl, furazolyl, oxathiazolyl, quinolinyl, isoquinolinyl, pyridopyrimidinyl, benzoxazolyl, benzimidazolyl, benzthiazolyl, benzoxazinyl, benzpyronyl, isoindolyl, or indolazinyl; and m and n each independently is an integer 0 to 2; or a therapeutically acceptable addition salt thereof; with the proviso that when R^1 is lower alkyl, cyclo(lower)alkyl or benzyl; R^2 is oxo or thioxo, R^3 is cyano, R^4 is lower alkyl and m and n are each 0, then R^9 is other than hydrogen, which comprises

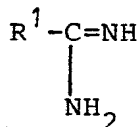
a) condensing a compound of formula VI



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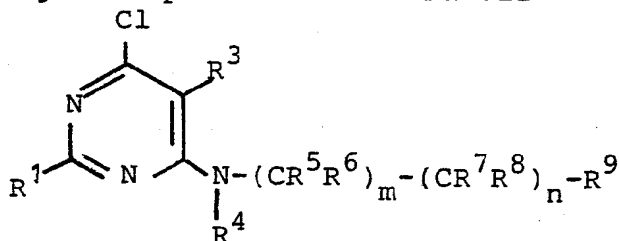
wherein R^3 is cyano, nitro, methylsulfonyl or amino-sulfonyl and R^4 to R^9 , m and n are as defined herein above and R^{10} is lower alkyl with an amidine of formula II



II

wherein R^1 is as defined hereinabove to give a compound of formula I wherein R^2 is oxo, R^3 is cyano, nitro methylsulfonyl or aminosulfonyl and R^1 , R^4 to R^9 , m and n are as defined hereinabove, or

b) reacting a compound of formula VII



(VII)

wherein R^1 , R^4 to R^9 , m and n are as defined hereinabove and R^3 is cyano, nitro, methylsulfonyl or amino-sulfonyl, with an aqueous ethanol solution of potassium hydroxide and hydrogen sulfide to give a corresponding compound of formula I wherein X is thioxo, or

c) reacting a compound of formula VII as defined above with a solution of an inert organic solvent containing an excess of ammonia to give a corresponding compound of formula I wherein R^2 is imino, or

d) hydrolysing a compound of formula I as defined hereinabove wherein R^3 is cyano to give a compound of formula I wherein R^3 is aminocarbonyl or

e) converting a compound of formula I as defined hereinabove to a therapeutically acceptable salt thereof.

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3. A process as claimed in Claim 1 for preparing a compound of formula I wherein R¹ is lower alkyl, cyclo(lower)alkyl or benzyl; R² is oxo, thioxo or imino; R³ is cyano or amino-carbonyl; R⁴, R⁶ and R⁸ each independently is hydrogen or lower alkyl; R⁵ and R⁷ are hydrogen; R⁹ is lower alkenyl, cyclo(lower)alkyl, 2,3 or 4-pyridinyl, 2 or 3-furanyl, 2 or 3-indolyl, 2 or 3-thienyl, 4-morpholinyl, phenyl or phenyl mono or disubstituted with hydroxy or lower alkoxy; and m and n each independently is an integer 0 to 2; or a therapeutically acceptable addition salt thereof.

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4. A process as claimed in Claim 1 for preparing a compound of formula I is lower alkyl, cyclo(lower)alkyl or benzyl; R^2 is oxo or thioxo, R^3 is cyano; R^4 , R^5 and R^7 are hydrogen; R^6 and R^8 each independently is hydrogen or lower alkyl; R^9 is lower alkenyl, 2, 3 or 4-pyridinyl, 2-furanyl, 3-indolyl, 3-thienyl, 4-morpholinyl, phenyl or phenyl mono- or disubstituted with lower alkoxy; and m and n each independently is the integer 0 or 1; or a therapeutically acceptable addition salt thereof.

5. A process as claimed in Claim 1 in which the compound of formula I prepared is

1,4-dihydro-2-methyl-4-oxo-6-[(3-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile; 1,4-dihydro-2-methyl-6-[N-methyl-N-(3-pyridinylmethyl)amino]-4-oxo-5-pyrimidinecarbonitrile; 1,4-dihydro-2-methyl-4-oxo-6-[(phenylethyl)amino]-5-pyrimidinecarbonitrile; 1,4-dihydro-2-methyl-4-oxo-6-[(2-pyridinylethyl)amino]-5-pyrimidinecarbonitrile; 1,4-dihydro-2-methyl-4-oxo-6-[(4-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile; 1,4-dihydro-2-methyl-4-oxo-6-[(2-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile; 1,4-dihydro-2-methyl-4-oxo-6-[(phenylmethyl)amino]-5-pyrimidinecarbonitrile; 1,4-dihydro-2-methyl-4-oxo-6-[2-(3-pyridinyl)ethylamino]-5-pyrimidinecarbonitrile; 1,4-dihydro-2-methyl-4-oxo-6-[2-(4-pyridinyl)ethylamino]-5-pyrimidinecarbonitrile; 1,4-dihydro-2-methyl-4-oxo-6-[(3-pyridinyl)amino]-5-pyrimidinecarbonitrile; 1,4-dihydro-2-methyl-6-[(3-pyridinylmethyl)amino]-4-thioxo-5-pyrimidinecarbonitrile; 1,4-dihydro-2-ethyl-4-oxo-6-[(3-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile; 1,4-dihydro-2-(1-methylethyl)-4-oxo-6-[(3-pyridinylmethyl)-

amino]-5-pyrimidine-carbonitrile; 2-cyclopropyl-1,4-dihydro-4-oxo-6-[(3-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile; 1,4-dihydro-2-(1,1-dimethylethyl)-4-oxo-6-[(3-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile; 1,4-dihydro-4-oxo-2-phenylmethyl-6-[(3-pyridinylmethyl)amino]-5-pyrimidinecarbonitrile; or a pharmaceutically acceptable salt thereof.

6. A process as claimed in Claim 1 in which the compound of formula I prepared is
1,4-dihydro-6-[(2-furanylmethyl)amino]-2-methyl-4-oxo-5-pyrimidinecarbonitrile; 1,4-dihydro-2-methyl-6-[[2-(4-morpholinyl)ethyl]amino]-4-oxo-5-pyrimidinecarbonitrile; 1,4-dihydro-2-methyl-4-oxo-6-[[2-(3-thienyl)ethyl]amino]-5-pyrimidinecarbonitrile; 1,4-dihydro-6-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-methyl-4-oxo-5-pyrimidine-carbonitrile; 1,4-dihydro-6-[[2-(1H-indol-3-yl)ethyl]amino]-2-methyl-4-oxo-5-pyrimidinecarbonitrile; 1,4-dihydro-2-methyl-4-oxo-6-[(2-propenyl)amino]-5-pyrimidinecarbonitrile; or a pharmaceutically acceptable addition salt thereof.

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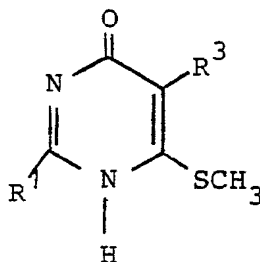
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7. A process for preparing a pharmaceutical composition which comprises bringing a compound of formula I as defined in Claim 1 or a therapeutically acceptable salt thereof into a form suitable for therapeutic administration.

8. A process as claimed in Claim 7 in which the composition also comprises an agent commonly used in treatment of congestive heart failure.

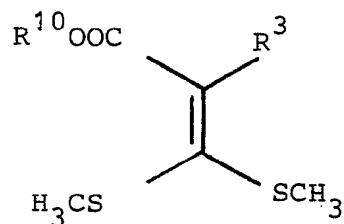
9. A process as claimed in Claim 8 in which said agent is selected from isosorbide dinitrate, captopril, nifedipine, hydralazine, prazosin, hydrochlorothiazide, furosemide, spironolactone, digitalis and dobutamine.

10. A process for preparing a compound of formula IV



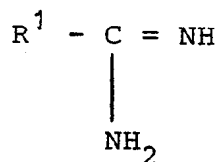
(IV)

in which R^1 is lower alkyl, cyclo(lower)alkyl, phenyl (lower)alkyl or trifluoromethyl, and R^3 is cyano, nitro, methylsulfonyl or aminosulfonyl which comprises condensing a compound of formula III



(III)

with a compound of formula II,



(II)

in which formulae R^1 and R^3 are as defined above and R^{10} represents lower alkyl.



European Patent
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EUROPEAN SEARCH REPORT

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Application number

| DOCUMENTS CONSIDERED TO BE RELEVANT | | | EP 84304158.3 |
|--|---|--|---|
| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int. Cl. 3) |
| D,A | DD - A - 72 790 (THOMAS) * Claim * | 1,5 | A 61 K 31/505 C 07 D 401/12 |
| | -- | | C 07 D 239/47 |
| A | AU - B1 - 22 870/77 (THE WELLCOME F.) * claim 1 * | 1,5 | C 07 D 239/56 C 07 D 405/12 C 07 D 409/12 C 07 D 403/12 |
| | -- | | |
| A | CHEMICAL ABSTRACTS, vol. 94, no. 9, March 2, 1981, Columbus, Ohio, USA A. KUMAR et al. "A novel and convenient synthesis of 2-amino-4-(N-alkyl-N-arylamino/pyrimidines..." page 723, column 1, abstract-no. 65 606n & Synthesis, (9), 748-51 (1980) | 1,5 | |
| | -- | | |
| A | EP - A1 - 0 005 984 (SMITH KLINE) * Abstract * | 1,2,5 | TECHNICAL FIELDS SEARCHED (Int. Cl. 3) C 07 D 401/00 C 07 D 239/00 C 07 D 403/00 C 07 D 405/00 C 07 D 409/00 A 61 K 31/00 |
| | -- | | |
| A | GB - A - 932 674 (ICI) * Claim 1 * | 1 | |
| | -- | | |
| A | US - A - 4 224 327 (MASSAROLI) * Abstract * | 12 | |
| | ---- | | |
| The present search report has been drawn up for all claims | | | |
| Place of search VIENNA | | Date of completion of the search 02-10-1984 | Examiner HOCHHAUSER |
| CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document | | | |